PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 44 MAY 2004

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.

Amendments to the EC Directive published

Amendments to Council Directive 2001/83/EC which includes requirements for advertising, Articles 86 to 100, have now been published in the Official Journal (L136) 30 April 2004 (Articles 61-71) http://pharmacos.endra.org/F2/review/doc/final pub/Dir 2004 27 20040430 EN.pdf.

Member states are required to implement the amendments in national law by October 2005. In relation to promotion to health professionals, the amendments are mainly minor but some will need to be incorporated into the Code. The Authority will examine the amendments in detail and discuss implementation with the ABPI and others, including the Medicines and Healthcare products Regulatory Agency. The amendments include a requirement that the Commission shall, following consultation with patients', consumers', doctors' and pharmacists' organisations, member states and other interested parties, present to the European Parliament and the Council a report on current practice with regard to the provision of information, particularly on the Internet, and its risks and benefits for patients.

Size matters

When responding to a complaint companies are asked to provide originals or colour photocopies of the materials at issue. Please remember that if a photocopy of material is provided it is very important that it should be copied at the same size as the original. Photoreducing material might render the prescribing information illegible and photoenlarging an abbreviated advertisement might make it appear to be in breach of the size restrictions referred to in Clause 5.3 of the Code.

Certification

Clause 14.1 of the Code requires that promotional material must not be issued until the final form of material, to which no subsequent amendments will be made, has been certified. A couple of problems have arisen recently and companies are reminded that it is not sufficient to certify the advertisement only after it has appeared. Nor is it sufficient to only certify one size of an advertisement which appears in different sizes eg A4 and A3. Each size and layout must be separately certified.

Practices charging representatives

The Authority has recently received details of practices charging representatives for attending meetings. The meetings are held in the practice and range from coffee mornings to lunch meetings. When sufficient information is available the Authority will write to the practices to highlight the requirements of the Code. These include Clause 15.3 which states that: 'Representatives must not employ any inducement or subterfuge to gain an interview. No fee should be paid or offered for the grant of an interview.' and the supplementary information, Donations to Charities, which states that donations to charities in return for representatives gaining interviews are prohibited. Further supplementary information to the same clause, headed General Medical Council (GMC), states that the GMC advises doctors that 'You must act in your patients' best interests when making referrals and providing or arranging treatment or care. So you must not ask for or accept any inducement, gift or hospitality which may affect or be seen to affect your judgement'.

The above reflects and expands upon UK and EC legal requirements which apply to both health professionals and pharmaceutical companies.

A medical representative who agreed to give money in exchange for appointments with GPs would be in breach of the Code. This would be so regardless of the purpose to which the money would be used.

Clause 19 of the Code relates to meetings and hospitality. The supplementary information to Clause 19.1 states, *inter alia*, that the impression that is created by the arrangements for

Practices charging representatives *continued*

any meeting must always be kept in mind. With regard to requests for support for coffee mornings, companies are reminded that meetings organised for groups of doctors, other health professionals and/or for administrative staff which are wholly or mainly of a social or sporting nature are unacceptable. Clause 19.2 prohibits payments to doctors or groups of doctors, either directly or indirectly, for rental for rooms to be used for meetings. This is not permissible even if such payment is made to equipment funds or patients' comforts funds and the like or to charities or companies.

The identity of the pharmaceutical company providing information to the Authority about inappropriate requests for payments is not revealed. Companies receiving such requests are invited to forward them to the Authority.

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, 17 September

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

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

MHRA publication of decisions

The Medicines and Healthcare products Regulatory Agency (MHRA) has started to publish summaries of the outcomes of complaints it has considered about advertising (www.medicines.mhra.gov.uk). The MHRA investigates complaints about both the promotion of over-the-counter medicines to the public and medicines promoted for prescribing.

How to contact the Authority

Our address is:

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

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

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

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

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

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

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

CASE AUTH/1520/9/03

ASHBOURNE v STRAKAN

Isotard 'Dear Doctor' letter

Ashbourne complained about a 'Dear Doctor' letter about Isotard (isosorbide 5 mononitrate (ISMN) 60mg) issued by Strakan. Ashbourne explained that until mid 2003 Strakan had supplied the company with ISMN 60mg tablets which it marketed as Isib. Strakan marketed the same tablets as Isotard. That agreement between the two companies had ended and so Ashbourne had found an alternative supplier; in agreement with the Medicines and Healthcare products Regulatory Agency (MHRA) the Isib brand would still be available, identified as a revised formulation. Ashbourne stated that by informing prescribers of '… an important change to a medicine that you may be prescribing' and then advising them that '… Isib … will be changing … in terms of … tablet type …', 'the only way to ensure that your patients continue to receive EXACTLY the same product … will be to change to the brand Isotard XL' and '[to] … ensure … that patients continue to receive the same medicine …', the letter lacked balance, fairness and objectivity. In particular it lacked information about the description of the tablet, its bioavailability and the nature of the formulation changes. Without this information the reader could infer that unless they switched to Isotard, they would in future be prescribing an inferior product for their patients, which was incorrect.

The Panel noted that the 'Dear Doctor' letter informed readers that although Isotard XL and Isib had been exactly the same product, differing only in their brand name, Isib was to change in terms of manufacturer and tablet type. Prescribers who thus wanted to ensure that patients currently taking Isib continued to receive exactly the same product, would have to switch them to Isotard XL. Strakan had held the marketing authorization for both Isotard XL and Isib. Isib was removed from Strakan's marketing authorization on 4 September 2003. The letter in question was dated 16 September.

The Panel considered that the information given in the letter about the changes to Isib was factual. It was true that the product was going to change and that in future it would no longer be identical to Isotard XL. The Panel did not consider that, in that regard, the letter lacked balance, fairness or objectivity. Nor did the Panel consider that the letter inferred that the reformulated Isib would be an inferior product. Strakan had sent the letter after its marketing authorization had been changed. The Panel ruled no breach of the Code.

Upon appeal by Ashbourne, the Appeal Board noted that Ashbourne had sent letters regarding changes to Isib to a select number of prescribers, wholesalers and pharmacists on 11/12 September, and then to others on 27 September. Ashbourne's representative also stated that the new Isib formulation would have been available to patients by 14/15 September. The Appeal Board noted Strakan's 'Dear Doctor' letter stated that 'This change [to Isib] is expected to occur over the coming months' and considered that as the new Isib formulation was already available by the time the letter was sent, this statement was inaccurate. Ashbourne's letters announcing the changes to Isib stated that the new tablet was of 'similar shape and appearance but is slightly larger than the existing tablet'. The Appeal Board queried whether this constituted a change in tablet type as anticipated by Strakan and referred to in the letter in question. The Appeal Board also noted Ashbourne's submission that Eumon 60XL was identical to the original Isib tablets. Eumon 60XL was listed in Chemist and Druggist Monthly Price List, January 2004, and as such would be available nationally. Notwithstanding Strakan's statement that there had been no reported sales of Eumon 60XL the Appeal Board considered that the statement '… the only way to ensure your patients continue to receive EXACTLY the same product as they have historically will be to change to the brand Isotard XL' was factually incorrect in light of the availability of Eumon 60XL. The Appeal Board considered that Strakan's letter contained some factual inaccuracies and thus ruled a breach of the Code.

Ashbourne alleged that Strakan had disparaged Ashbourne by making an announcement about changes to Isib, when it was Ashbourne's and/or the marketing authorization holder's responsibility to do so, and Strakan had done so in a way that was neither balanced, fair or objective.

The Panel noted that the change to Isib affected Strakan too as Isib had to be removed from Strakan's marketing authorization for ISMN. The letter gave no details of the change which was to occur to Isib but only noted that whereas Isib and Isotard XL had been the same product in the past, they would be different in future. The Panel did not consider such a statement disparaged Ashbourne or Isib. No breach of the Code was ruled.

Upon appeal by Ashbourne, the Appeal Board considered that although the letter had referred to changes to Isib the statements made, although ruled in breach of the Code above, had not disparaged Ashbourne or Isib. The Appeal Board upheld the Panel's ruling of no breach of the Code.

Ashbourne stated that the letter purported to be an announcement, in order to gain the reader's attention, but was really promotional material. The letter referred to pricing arrangements and to the other dosages available, information which was not relevant in the context of an announcement about changes to Isib.

The Panel did not consider that the 'Dear Doctor' letter was disguised promotion; it was written on company headed note paper and signed by a Strakan member of staff. In the Panel's view the letter clearly promoted Isotard XL in the context of the impending changes to Isib. No breach of the Code was ruled.

Ashbourne stated that it brought discredit to and reduced confidence in the pharmaceutical industry if prescribers were informed of product changes other than by means of factual, accurate and informative

announcements made by or with the approval of the marketing authorization holder and where appropriate, as in this case, under the guidance of the MHRA. By making its own announcement Strakan had put at risk the effectiveness of the announcements issued by Ashbourne with the agreement of the marketing authorization holder and under the guidance of the MHRA.

The Panel noted its comments and rulings above. The Panel did not consider that the 'Dear Doctor' letter brought discredit upon or reduced confidence in the pharmaceutical industry. The impending changes to Isib also affected Strakan and its marketing authorization for ISMN. A ruling of a breach of Clause 2 was a sign of particular censure and reserved for such use. No breach of that clause was ruled. Upon appeal by Ashbourne this ruling was upheld.

Ashbourne Pharmaceuticals Ltd complained about a 'Dear Doctor' letter about Isotard (isosorbide 5 mononitrate (ISMN) 60mg) issued by Strakan Limited. The letter had been sent to dispensing GPs' practices.

Background information from Ashbourne

Ashbourne explained that until mid June 2003 Strakan supplied ISMN 60mg tablets to Ashbourne, which Ashbourne marketed under Ashbourne livery and the Ashbourne trade mark 'Isib', as a distributor named on Strakan's marketing authorization. Strakan also marketed the same product under its livery and 'Isotard' trade mark. As a result of commercial differences that arose earlier in 2003, the supply agreement between Ashbourne and Strakan was terminated by mutual agreement, leaving Ashbourne with approximately 4 months' stock of the Strakan supplied product, which Ashbourne sold until supplies were exhausted in late August.

Shortly after the termination of the supply agreement a new manufacturer, which Ashbourne had been in discussion with, submitted an application to the Medicines and Healthcare products Regulatory Agency (MHRA) for a variation of its marketing authorization to permit Ashbourne to market its ISMN 60mg tablets under Ashbourne livery and the 'Isib' trade mark. Following discussions between the MHRA, the manufacturer and Ashbourne, the variation was approved, on the condition that the product was identified on the pack as having a revised formula and known prescribers of Isib were informed. Ashbourne co-operated fully with the MHRA's requirements and announcements were issued to relevant doctors, pharmacists and wholesalers (copies were supplied).

Ashbourne's 'Dear Doctor' announcement, noted that there were differences between the formulation of Strakan's product and the new manufacturer's product. The announcement, the text of which was drafted in consultation with the MHRA, drew this to doctors' attention and provided reassurance that both the old and new formulation were bio-equivalent to Imdur, the original AstraZeneca brand of ISMN.

During the week commencing 15 September 2003 Ashbourne's marketing department received reports that Strakan representatives had told surgeries that: Strakan had terminated its supply agreement with Ashbourne; Isib was no longer available; Isib had been replaced by Isotard and Isib had been discontinued.

The first point was correct but it was an item of confidential information, the disclosure of which was prohibited by the terms of an agreement between Strakan and Ashbourne. The other points were not correct.

Background information from Strakan

Strakan explained that between 8 April 2002 and 4 September 2003, as a result of a commercial agreement, Ashbourne was allowed to promote Isib to dispensing doctors as a named distributor under Strakan's marketing authorization in the UK. As stated by Ashbourne, commercial differences between the companies, following the distribution of Isib outside the dispensing doctor market, led to the termination of the contract between Ashbourne and Strakan in June 2003. Subsequent to the termination, at Ashbourne's specific request, Strakan formally approached the MHRA to initiate removal of all registered sites for Ashbourne Pharmaceuticals Limited and the trade name Isib 60XL from Strakan's 60mg ISMN marketing authorization (PL 16508/0022). These names were removed from Strakan's marketing authorization on 4 September 2003. Ashbourne had never informed Strakan of any of its intentions regarding future plans for the Isib brand name. Strakan sent the 'Dear Doctor' letter at issue to dispensing doctors outlining the change to its marketing authorization agreed with the MHRA.

The points raised by Ashbourne about the conduct of Strakan's representatives were inaccurate and without foundation. The Strakan representatives were not briefed to state that Isib was no longer available nor that it had been replaced or discontinued. Strakan noted that Ashbourne had failed to supply any specific details of its allegations.

1 Alleged breach of Clause 7

COMPLAINT

Ashbourne stated that by purporting to inform prescribers of '…an important change to a medicine that you may be prescribing' and then advising them that '…Isib …will be changing ….in terms of…tablet type…', '... the only way to ensure that your patients continue to receive EXACTLY the same product …will be to change to the brand Isotard XL' and '[to]…ensure…that patients continue to receive the same medicine…', the letter lacked balance, fairness and objectivity. In particular it lacked important and reassuring information about the description of the tablet, its bioavailability and the nature of the formulation changes. Without this information the reader could infer that unless they switched to Isotard, they would in future be prescribing an inferior product for their patients, which was incorrect. Patients might, for instance, be more concerned by a switch of brand than by a revision to the formulation.

RESPONSE

Strakan stated that Ashbourne had failed to support its allegation that the 'Dear Doctor' letter lacked 'balance, fairness and objectivity'; it had not provided any specific evidence as to why this might be the case. All information and claims within the letter related solely to Strakan's marketing authorization. There were no comparisons with any other products covered by any other company's marketing authorizations. It did not contain any information about new products carrying the Isib brand name as Strakan was not privy to any information about Ashbourne's reformulated, re-authorized Isib. Strakan did not understand why Ashbourne expected it to have included 'important and reassuring information' relating to a product about which the company had no information and over which it had no control. It was particularly difficult to understand why Ashbourne suggested that the letter 'could infer' that Isib was an inferior product when no such comparison was made. The final statement by Ashbourne that 'patients might, for instance, be more concerned by a switch of brand than by a revision to the formulation' might or might not be true, but Strakan failed to see its relevance. The letter at issue was not sent to patients but to prescribers, recognising their role in discussing with patients the issues around proposed changes to modified release medicines on which they might be stabilised. Strakan was only able to inform these discussions with information relating to changes in its own marketing authorization, which were essentially changes to brand names and not to its formulation. The National Prescribing Centre had also recognised the importance of ensuring that patients received the modified release preparation intended by the prescriber when it stated 'For those limited situations where an MR [modified release] preparation is appropriate, it is important that the correct preparation, ie that intended by the prescriber, is dispensed. As confusion can arise if such prescriptions are written generically, it seems sensible to recommend brand name prescribing for MR preparations. Of more importance is the problem that different MR preparations of the same drug have different release characteristics. Therefore bioequivalence cannot be assumed and all MR preparations are licensed by brand name' (MeReC bulletin, II(4): 2000).

Implicit in this opinion was the assumption that certain brand names were associated with specific formulations. Thus Strakan considered that changes to brand names could have clinical implications and that clinicians should be aware of such changes.

PANEL RULING

The Panel noted that the 'Dear Doctor' letter informed readers that although Isotard XL and Isib had been exactly the same product, differing only in their brand name, Isib was to change in terms of manufacturer and tablet type. Prescribers who thus wanted to ensure that patients currently taking Isib continued to receive exactly the same product, would have to switch them to Isotard XL. Strakan had held the marketing authorization for both Isotard XL and Isib. Isib was removed from Strakan's marketing authorization on 4 September 2003. The letter in question was dated 16 September.

The Panel considered that the information given in the letter about the changes to Isib was factual. It was true that the product was going to change and that in future it would no longer be identical to Isotard XL. The Panel did not consider that, in that regard, the letter lacked balance, fairness or objectivity. Nor did the Panel consider that the letter inferred that the reformulated Isib would be an inferior product. Strakan had sent the letter after its marketing authorization had been changed.

The Panel noted that Ashbourne had not cited a sub-clause of Clause 7 but considered that the allegation referred to the requirements of Clause 7.2 of the Code. No breach of that clause was ruled.

APPEAL BY ASHBOURNE

With regard to Strakan's point in its background comments about sales of Isib outside of the dispensing doctor market, Ashbourne noted that it had made no admissions in its complaint as to the reasons that commercial differences arose.

Ashbourne noted that the 'Dear Doctor' letter had made forward-looking statements relating to the future of Isib in relation to two features; change of manufacturer and change of the tablet type.

Ashbourne noted that in its response below to an alleged breach of Clause 2, Strakan had stated that it '…had no knowledge of Ashbourne's intentions regarding its brand name including any announcements that it might wish to issue relating to any new formulations, marketing authorizations, or supply agreements', and the letter was sent to '… clarify changes to its marketing authorization …not to give information about future uses of the Isib brand name, about which [it] knew nothing'.

Ashbourne considered that as Strakan had admitted that it was not aware of what was planned for the future of Isib, it was now clear that the letter presented speculation about what might happen as facts about what would happen. In fact, there were a number of possible options to explore, including to approach Valpharma SpA (the San Marino based company that manufactured the product marketed under the Strakan marketing authorization) to supply the same product, sell the Isib trade mark and leave the isosorbide mononitrate market or approach an alternative manufacturer. All that Strakan had known for certain was that Isib, as sold under the Strakan marketing authorization, would, after all remaining stock had been exhausted, cease to be available, thereafter it would remain available under the Strakan brand and any enquiries concerning Isib could be directed to Ashbourne. If Strakan had considered that that was not sufficiently informative, and that prescribers required information about future plans for Isib, it was open to Strakan to approach Ashbourne to ask it to co-operate in the production of either a joint announcement or separate announcements in terms acceptable to all parties

concerned. Alternatively, Strakan could have approached the MHRA for guidance on what it could have said about the future of Isib. However, Strakan had failed to provide evidence that it had sought the guidance of the MHRA on this point.

Ashbourne stated that its appeal was based on the following grounds:

Firstly, at the time of writing the letter Strakan had not had the requisite factual knowledge upon which to base the forward-looking statements about the future of Isib. Statements about a change of manufacturer and tablet type should not therefore have been presented as fact, when Strakan knew or ought to have known that those statements were uncorroborated and amounted to no more than speculation or opinion. The Panel had erred in finding that the letter was factual at least in relation to the first paragraph, as that finding was contrary to Strakan's admissions as to its lack of knowledge of plans for Isib.

Secondly, uncorroborated statements about the future of Isib and features of the replacement product should not have been included in the letter because they related to a product marketed or to be marketed under a third party's marketing authorization and only Ashbourne and the relevant marketing authorization holder could have known, and be in a position to provide prescribers with, all of the requisite information about the replacement product. The statements about change of manufacturer and tablet type were uncorroborated speculation or opinion as to what might happen to Isib rather than a statement of what Strakan knew would happen. Further, the forward-looking statements about the future of Isib were neither fair, because they were uncorroborated speculation about the future presented as fact, nor objective because they posed questions in the reader's mind (what were the implications of a change in manufacturer and/or tablet type?) without presenting any factual information from which the reader could objectively assess the clinical implications of the changes.

Ashbourne noted that on the issue of objectivity, Strakan had stated in its response that 'All information and claims within the letter related solely to Strakan's marketing authorization. There were no comparisons with any other products covered by any other company's marketing authorizations. It did not contain any information about new products carrying the Isib brand name …'. Ashbourne alleged, however, that the letter had drawn attention to two properties of Isib (manufacturer and tablet type) in the context of announcing '… an important change to a medicine that you may be prescribing …' thereby informing the reader that there might be differences between the product marketed under the Strakan marketing authorization and the replacement product marketed under a third party's marketing authorization. But, it failed (presumably because Strakan had no information about the replacement product) to present any comparative data upon which readers could make a judgement about the significance of the differences identified. Strakan had quite rightly noted that '… different MR preparations of the same drug have different release characteristics. Therefore bioequivalence could not be assumed…'. Ashbourne considered that prescribers, having been informed of an impending change of manufacturer, would need to have, *inter alia*, comparative information about bioequivalence, so that they might assess whether the change of manufacturer was of clinical significance. This information was not presented by Strakan. Conversely Ashbourne's announcement had clearly stated that 'Both the current Isib 60XL product and the new formulation have been shown to be bioequivalent to Imdur tablets'. Ashbourne considered that its announcement had provided the necessary and reassuring comparative information about bioequivalence.

Ashbourne stated that the same point could be made in relation to tablet type. Strakan had drawn attention to changes in tablet type but presented no comparative information as to any relevant differences between the product marketed under the Strakan marketing authorization and the replacement product, again presumably because it had no knowledge of the differences. Again Ashbourne's announcement had provided comparative information about changes to excipients.

Ashbourne alleged that in relation to factual accuracy, having undertaken further research, it was now aware that the isosorbide mononitrate marketed under the Strakan marketing authorization was manufactured by Valpharma SpA of San Marino and the same product was also marketed in the UK by Valpharma as Eumon 60XL. Therefore the claim that '… the only way to ensure your patients continue to receive EXACTLY the same product as they have historically will be to change to the brand Isotard XL' was factually incorrect.

COMMENTS FROM STRAKAN

Strakan submitted that the appeal did not in any way strengthen or advance the original complaint; it stood by its response to the complaint and considered that the Panel had reached the only reasonable conclusion that could be made.

Ashbourne's appeal appeared to have moved away from a general complaint that Strakan had no right to discuss Isib in the 'Dear Doctor' letter, to a more specific complaint that it should not have stated that '… Isib … would be changing both in terms of the manufacturer and tablet type'. In response to this change in the position Strakan reiterated its response to the complaint. The letter had contained information about changes to a marketing authorization which had belonged to Strakan. The changes, which had been agreed with the MHRA, were the removal of all registered sites for Ashbourne Pharmaceuticals Ltd and the trade name Isib 60XL. Strakan submitted that as a result of conversations and discussions with Ashbourne, it was content that changes to manufacturer and tablet type would also be taking place and that these changes would occur over the coming months. Strakan had stated this expectation in its letter and these changes subsequently occurred. Strakan noted that once Isib was removed from its marketing authorization Ashbourne was free to do with its brand name as it

wished. Strakan submitted however, that its letter referred to changes, and anticipated changes, to the products as listed on its own marketing authorization, about which it had a right to provide information and advance notice to its customers.

Strakan noted that Ashbourne had now raised a new point of 'factual accuracy' which had not appeared in its original complaint. Eumon 60XL was licensed in the UK but no sales had ever been registered (source IMS, December 2003). Strakan submitted that, based on its knowledge at the time, '… the only way to ensure your patients continue to receive EXACTLY the same product as they have historically will be to change to the brand Isotard XL' was, and continued to be, a reasonable statement. Strakan noted that Ashbourne's statement that 'the isosorbide mononitrate marketed under the Strakan marketing authorization was manufactured by Valpharma SpA of San Marino' was wrong. In fact, the 60mg strength of this tablet was manufactured by Valpharma International SpA, Pennabilli, Italy, and this had been the case since approval of the change to the marketing authorization in June 2003.

FURTHER COMMENTS FROM ASHBOURNE

Ashbourne did not accept that the basis of its complaint had changed. To the extent that it was necessary for Strakan to inform prescribers of changes to Strakan's marketing authorization, Strakan had had a right to discuss Isib. The basis of the complaint was that the letter at issue had also dealt with matters that it was not necessary or appropriate for Strakan to inform prescribers of, either because they were not based on facts within Strakan's own knowledge, and/or because they were matters that it was for Ashbourne and/or a third party marketing authorization holder for any replacement product to inform prescribers of in the light of decisions to be made that that had not involved Strakan.

Ashbourne stated that central to its complaint was the issue of factual accuracy, in particular whether certain matters asserted in the letter were facts within Strakan's knowledge, or whether they amounted to no more than speculation or opinion, presented as fact.

Ashbourne noted that Strakan had not presented any evidence against its proposition that the letter contained forward-looking statements relating to Isib which were no more than speculation or opinion presented as fact. Ashbourne considered that Strakan's response to the appeal that the letter referred to '… changes, and anticipated changes, to the products as listed on our own [marketing authorization], about which it had a right to provide information and advance notice …' lent further support to Ashbourne's case. Ashbourne concluded that Strakan, by referring to its intention to give advance notice of 'anticipated changes', accepted that certain of the matters stated in the letter were outside of its actual knowledge and were therefore speculation or opinion about the future. Further, Strakan now contended that its 'knowledge' of changes to manufacturer and tablet type was the result of '… conversations and discussions with Ashbourne…'. Ashbourne stated that, however, for commercial reasons, it had not informed Strakan of its plans to find an alternative supplier for Isib and it was inconceivable that Strakan knew of its commercial strategy for Isib following the ending of the commercial relationship.

Ashbourne noted that Strakan had not presented any evidence against its assertion that the isosorbide mononitrate marketed under Strakan's marketing authorization was the same as Eumon 60XL, marketed in the UK by Valpharma, and that the claim that '… the only way to ensure that your patients continue to receive EXACTLY the same product as they have historically will be to change to the brand Isotard XL' was factually incorrect. Instead, Strakan now contended that it was reasonable to make this claim because no sales of Eumon 60XL had been recorded by IMS. Ashbourne stated that it had, however, recently been able to purchase a pack from a retail pharmacy in the UK.

APPEAL BOARD RULING

The Appeal Board noted that the 'Dear Doctor' letter informed readers that although Isotard XL and Isib had been exactly the same product, differing only in their brand name, Isib was to change in terms of manufacturer and tablet type. Prescribers who thus wanted to ensure that patients currently taking Isib continued to receive exactly the same product, would have to switch them to Isotard XL.

Strakan's letter was dated 16 September. The Appeal Board noted from Ashbourne's representative that Ashbourne's 'Dear Pharmacist', 'Dear Doctor' and general letter regarding changes to Isib had been sent to a select number of prescribers, wholesalers and pharmacists on 11/12 September, and then to others on 27 September. The Appeal Board also noted from the Ashbourne representative that supplies of the new Isib formulation were with wholesalers by 11/12 September and that the product would have been available to patients by 14/15 September. The Ashbourne representative stated that the old stock was to be used up and the wholesaler stock was run down before the new formulation was distributed. The Appeal Board noted Strakan's comment in its 'Dear Doctor' letter that 'This change [to Isib] is expected to occur over the coming months'. The Appeal Board considered that as the new Isib formulation was already available by the time Strakan's 'Dear Doctor' letter was sent, this statement was inaccurate.

The Appeal Board noted from Ashbourne's letters announcing the changes to Isib that the new Isib tablet was of 'similar shape and appearance but is slightly larger than the existing tablet'. The Appeal Board queried whether this constituted a change in tablet type as anticipated by Strakan and referred to in the letter in question.

The Appeal Board noted Ashbourne's submission that Eumon 60XL was identical to the original Isib tablets. Eumon 60XL was listed in Chemist and Druggist Monthly Price List, January 2004, and as such would be available nationally. Notwithstanding Strakan's statement that there had been no reported sales of

Eumon 60XL the Appeal Board considered that the statement '… the only way to ensure your patients continue to receive EXACTLY the same product as they have historically will be to change to the brand Isotard XL' was factually incorrect in light of the availability of Eumon 60XL.

The Appeal Board considered that Strakan's letter contained some factual inaccuracies and thus ruled a breach of Clause 7.2 of the Code. The appeal on this point was successful.

2 Alleged breach of Clause 8

COMPLAINT

Ashbourne stated that this was an extension of the issues raised in points 1 above and 4 below. It was disparaging of Ashbourne for Strakan to purport to make an announcement about changes to an Ashbourne product, when it was Ashbourne's and/or the marketing authorization holder's responsibility to do so; and Strakan had done so in a way that was neither balanced, fair or objective.

RESPONSE

Strakan noted that once again Ashbourne stated that the 'Dear Doctor' letter referred to an Ashbourne product. Strakan reiterated that the letter referred only to changes in the Strakan marketing authorization. Once again Ashbourne repeated the accusation that the letter 'was neither balanced, fair or objective' without providing any supportive evidence or explanation.

PANEL RULING

The Panel noted that although Ashbourne's product, Isib, was about to change, that change affected Strakan too as Isib had to be removed from Strakan's marketing authorization for ISMN. The letter gave no details of the change which was to occur to Isib but only noted that whereas Isib and Isotard XL had been the same product in the past, they would be different in future. The Panel did not consider such a statement disparaged Ashbourne or Isib. No breach of Clause 8.1 was ruled.

APPEAL BY ASHBOURNE

Ashbourne stated that the Panel was incorrect in its finding that the changes to Isib affected Strakan, if by that it had meant that they did not also affect Ashbourne and/or the replacement product's marketing authorization holder. The only change that affected Strakan was the removal from the Strakan marketing authorization of Ashbourne's name as an own label distributor under the Isib brand. Ashbourne accepted that it was proper for Strakan to inform precribers of this, although it was by no means common practice. Ashbourne contended that the Panel had failed to recognise that if Ashbourne decided to find an alternative manufacturer and market Isib as an own label supplier under that manufacturer's marketing authorization, then any announcement to prescribers about the change of manufacturer and any other relevant changes, such as tablet type, would be a matter for Ashbourne and the new manufacturer. Ashbourne stated that it did this after seeking guidance from the MHRA as to the form of the announcement. By purporting to provide prescribers with information about the replacement product, Strakan had stepped over the limits of its responsibility into the area of responsibility of Ashbourne and/or the new manufacturer. This was disparaging because it effectively usurped Ashbourne's responsibilities in front of prescribers.

Ashbourne also stated that the Panel was incorrect in its finding that the letter had given no details of the change which was to occur to Isib. It had given specific details, namely of a change in manufacturer and tablet type.

COMMENTS FROM STRAKAN

Strakan considered that Ashbourne's appeal added nothing further to its original complaint. However, Ashbourne's claim in its letter to doctors and pharmacists that its new formulation of Isib was bioequivalent to Imdur, had not meant that its new formulation was bioequivalent to the previous formulation of Isib or to Isotard XL.

FURTHER COMMENTS FROM ASHBOURNE

Ashbourne agreed with Strakan's point regarding bioequivalence but considered it disingenuous. Ashbourne noted that Strakan's letter gave no information about bioequivalence, whereas its own announcements, agreed with the MHRA, had given relevant information about bioequivalence.

APPEAL BOARD RULING

The Appeal Board considered that although the letter had referred to changes to Isib the statements made, although ruled in breach of the Code at point 1 above, had not disparaged Ashbourne or Isib. The Appeal Board upheld the Panel's ruling of no breach of Clause 8.1 of the Code. The appeal on this point was unsuccessful.

3 Alleged breach of Clause 10

COMPLAINT

Ashbourne stated that the letter purported to be an announcement, in order to gain the reader's attention, but was really promotional material. This was quite clear in paragraphs 3 and 4, which referred to pricing arrangements and to the other dosages available. None of that information was relevant in the context of an announcement about changes to Isib.

RESPONSE

Strakan stated that it was difficult to understand why Ashbourne considered that the letter was disguised promotion as it was written on Strakan headed paper, clearly contained information on Strakan's Isotard XL,

was signed by a member of Strakan's staff, and was accompanied by appropriate prescribing information. Strakan challenged Ashbourne's assertion that 'none of that information was relevant in the context of an announcement about changes to Isib' as it considered that the removal of the Isib brand name from the Strakan marketing authorization was relevant information and as such the company was entitled, and indeed obliged to include it in its letter.

PANEL RULING

The Panel did not consider that the 'Dear Doctor' letter was disguised promotion; it was written on company headed note paper and signed by a Strakan member of staff. In the Panel's view the letter clearly promoted Isotard XL in the context of the impending changes to Isib. No breach of Clause 10.1 was ruled.

4 Alleged breach of Clause 2

COMPLAINT

Ashbourne stated that it brought discredit to and reduced confidence in the pharmaceutical industry if prescribers were informed of product changes other than by means of factual, accurate and informative announcements made by or with the approval of the marketing authorization holder and where appropriate, as in this case, under the guidance of the MHRA. However, Strakan had purported to make its own announcement which was wholly inappropriate as it was not the marketing authorization holder for the revised formula Isib, but a competitor of the product's distributor, Ashbourne. By doing so Strakan had put at risk the effectiveness of the announcements issued by Ashbourne with the agreement of the marketing authorization holder and under the guidance of the MHRA.

RESPONSE

Strakan stated that it understood that rulings of breaches of Clause 2 were reserved for activities or materials which brought discredit upon, or reduced confidence in, the pharmaceutical industry, and that such rulings were signs of particular censure. As the company had defended itself against all the other allegations made by Ashbourne, it considered the allegation of a breach of Clause 2 to be wholly without foundation. Strakan noted the allegation that it had informed prescribers of product changes '… other than by means of factual, accurate and informative announcements made by or with the approval of the marketing authorization holder and where appropriate, as in this case, under the guidance of the MHRA'. However, Strakan considered that the 'Dear Doctor' letter at issue was factual, accurate and informative. The origin, content and purpose of the letter was very clear to the reader; Strakan repeated that it referred to changes that occurred to a marketing authorization which had been held by Strakan, not Ashbourne. Strakan had no knowledge of Ashbourne's intentions regarding its brand name including any announcements that Ashbourne might wish to issue relating to any new formulations, marketing authorizations or supply agreements. Strakan sent the 'Dear Doctor' letter to clarify the changes to its marketing authorization and to give information about Isotard, not to give information about future uses of the Isib brand name, about which the company knew nothing.

As Strakan was the prior marketing authorization holder, and as the letter was based on changes to its own marketing authorization following applications to, and approval by, the MHRA, Strakan considered that this allegation was completely insupportable and without foundation.

PANEL RULING

The Panel noted its comments and rulings above. The Panel did not consider that the 'Dear Doctor' letter brought discredit upon or reduced confidence in the pharmaceutical industry. The impending changes to Isib also affected Strakan and its marketing authorization for ISMN. A ruling of a breach of Clause 2 was a sign of particular censure and reserved for such use. No breach of that clause was ruled.

APPEAL BY ASHBOURNE

Ashbourne stated that Strakan's assertion that the letter was '…based on changes to our own marketing authorization following application to, and approval by, the MHRA…', required clarification. The changes agreed with the MHRA would have consisted of the removal from Strakan's marketing authorization of Ashbourne as an own label supplier under the Isib brand. As explained above, the 'Dear Doctor' letter did considerably more than merely convey that information. What required clarification was which parts of the letter were based on matters agreed with the MHRA and what evidence Strakan had to prove that those matters said to have been agreed with the MHRA were so agreed.

Ashbourne noted Strakan's submission that it '… had no knowledge of Ashbourne's intentions regarding its brand name including any announcements that Ashbourne might wish to issue relating to any new formulations, marketing authorizations or supply agreements' and that the letter was sent to '… clarify changes to its marketing authorization … not to give information about future uses of the Isib brand name, about which the company knew nothing'. Ashbourne alleged that despite this admitted lack of knowledge about the future of Isib, the letter had contained forward looking statements about the future of Isib, namely impending changes to manufacturer and tablet type which, given these admissions, were evidently not based on corroborated facts within Strakan's knowledge, but were speculation or opinion.

Ashbourne alleged that it was a matter for particular censure that a marketing authorization holder for one product should write to prescribers to inform it about its product and include in the letter an announcement about the impending availability of and features of a product marketed under a third party's marketing authorization, particularly when the information was uncorroborated speculation, not fact. Ashbourne

noted that had it failed to find an alternative manufacturer and left the market instead, Strakan would have been forced to issue a correction once it became aware of the true facts.

Ashbourne further noted that the information concerned matters which, if they were going to happen at all, should have been announced by Ashbourne and the replacement product's marketing authorization holder, if and when i) a decision was made as to Isib's future, ii) Ashbourne and the replacement product's marketing authorization holder had agreed marketing arrangements, iii) Ashbourne and the replacement product's marketing authorization holder had agreed the text of an announcement, iv) the MHRA had been consulted and v) the replacement product was approved for release to the market. Only when the full facts could be presented, supported by the summary of product characteristics, could information about the replacement product be issued.

COMMENTS FROM STRAKAN

Strakan submitted that an allegation of a breach of Clause 2 was wholly without foundation and the company had, at all times, sought to act with transparency and in good faith. Strakan submitted that it had striven to make decisions about its products and its marketing authorizations, and to inform its customers of these decisions, based on the best and most complete regulatory, clinical and commercial information at its disposal. Irrespective of Ashbourne's opinions of the 'Dear Doctor' letter, Strakan was extremely disappointed that it had sought to obtain a ruling of such particular censure. Strakan considered that this was an entirely inappropriate response.

Strakan submitted in conclusion, that it was entitled to give information to its customers about its own marketing authorization. At the time that the letter was written and sent, it contained no information other than that which Strakan, as marketing authorization holder, was entitled to provide about decisions which it had taken about its authorized products, based on the most accurate and up-to-date information which it had.

FURTHER COMMENTS FROM ASHBOURNE

Ashbourne would have agreed that Strakan had acted with '... transparency and good faith ...' had Strakan taken care to ensure that each statement in the letter was either factually accurate and within Strakan's own knowledge or suitably qualified where that was not the case eg in relation to events that Strakan anticipated would come to pass or conclusions it considered reasonable at the time.

Ashbourne would also have agreed that Strakan had acted with '… transparency and good faith ...' had Strakan not sought to announce matters which, if they were going to happen at all, should have been announced by Ashbourne and any replacement product's marketing authorization holder.

Ashbourne alleged that the statement 'At the time that the letter was written and sent, it contained no information other than that…about decisions which [Strakan] had taken about its authorized products …' illustrated the fundamental contradiction in Strakan's position. The letter presented statements about the future of Isib as if they were facts, when by its own admission such facts were not within Strakan's own actual knowledge and whether such 'facts' would ever come to be, depended not on decisions to be taken by Strakan in relation to Strakan's marketing authorization, but by Ashbourne and a third party, without Strakan's involvement.

APPEAL BOARD RULING

The Appeal Board did not consider that the 'Dear Doctor' letter brought discredit upon or reduced confidence in the pharmaceutical industry. A ruling of a breach of Clause 2 was a sign of particular censure and reserved for such use. The Appeal Board upheld the Panel's ruling of no breach of Clause 2. The appeal on this point was unsuccessful.

Complaint received **25 September 2003**

Case completed **2 February 2004**

CASE AUTH/1525/10/03

PIERRE FABRE v AVENTIS PHARMA

Taxotere folder

Pierre Fabre complained about the promotion of Taxotere (docetaxel) by Aventis Pharma. The material at issue, a folder aimed at oncology health professionals, compared the use of Taxotere plus cisplatin and vinorelbine plus cisplatin, for the first-line treatment of unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC). The folder detailed the design of the pivotal study (TAX 326) which had included three treatment arms: Taxotere plus cisplatin, vinorelbine plus cisplatin and Taxotere plus carboplatin. Taxotere was only licensed for use in combination with cisplatin. Page three of the folder featured graphs comparing the results of the first two arms of the study; no results were given for the Taxotere/carboplatin arm. A pocket in the folder included a reprint of Fossella *et al* (2003) which was the published report of the TAX 326 study. Pierre Fabre alleged that the folder enclosing a copy of Fossella *et al* promoted the use of the unlicensed combination of Taxotere plus carboplatin. Pierre Fabre supplied Navelbine (vinorelbine).

The Panel noted that in Case AUTH/1483/6/03 the Appeal Board had considered that, in the context of a factual statement regarding the design of the TAX 326 study, reference to the combination of Taxotere plus carboplatin did not constitute promotion of an unlicensed combination. The leavepiece at issue was not inconsistent with the Taxotere summary of product charcteristics (SPC) in that, as in the SPC, although the dosage and schedule details of the TAX 326 study were given, there was no reference to the outcome of treatment with Taxotere plus carboplatin. No breach of the Code was ruled. In the Panel's view this ruling was due to the context in which the description of the study design from Fossella *et al* had been presented. It had been important to the Appeal Board's decision that no outcome data for the Taxotere/carboplatin arm had been included in the leavepiece.

The Panel considered that in the present case, Case AUTH/1525/10/03, the folder, together with the copy of Fossella *et al*, provided more than the limited information given about the study in the leavepiece at issue in Case AUTH/1483/6/03. The copy of Fossella *et al* had been provided, unsolicited, in a promotional folder. The unsolicited provision of Fossella *et al* constituted promotion of the unlicensed combination of Taxotere plus carboplatin as alleged. A breach of the Code was ruled. Upon appeal by Aventis this ruling was upheld.

Pierre Fabre Ltd complained about the promotion of Taxotere (docetaxel) by Aventis Pharma Ltd. The material at issue was a folder (ref TAX 890/07/03) which according to Pierre Fabre had been collected on 20 September 2003 from Aventis' stand at the North of Scotland Lung Cancer site specific group. The folder, which was aimed at oncology health professionals, compared the use of Taxotere in combination with cisplatin and vinorelbine in combination with cisplatin, for the first-line treatment of unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC). The folder detailed the design of the pivotal study (TAX 326) which included three treatment arms: Taxotere plus cisplatin, Taxotere plus carboplatin and vinorelbine plus cisplatin. Taxotere was only licensed for use in combination with cisplatin. Page three of the folder featured graphs comparing the results of Taxotere plus cisplatin vs vinorelbine plus cisplatin. No results were given for the Taxotere/carboplatin arm of the study. A pocket in the folder included a reprint of Fossella *et al* (2003) which was the published report of the TAX 326 study.

Pierre Fabre supplied Navelbine (vinorelbine).

Pierre Fabre had previously complained about a Taxotere leavepiece which had also given details of the TAX 326 study, alleging that the description of the Taxotere/carboplatin arm amounted to promotion of an unlicensed indication (Case AUTH/1483/6/03). In that case the Panel did not accept Aventis' submission that it had to fully describe all three arms of the study in order to provide complete and accurate information. In the Panel's view it would have been sufficient to state that the study was a three arm study without giving details of the unlicensed Taxotere/carboplatin regimen. The Panel considered that the inclusion of such information constituted promotion of an unlicensed combination. A breach of the Code had been ruled.

Upon appeal by Aventis, the Appeal Board noted that the Taxotere summary of product characteristics (SPC) gave the dosage and schedule details of the TAX 326 study. The description of the study in the leavepiece was not inconsistent with the SPC; as in the SPC no reference to the outcome of treatment with Taxotere and carboplatin was given. The Appeal Board considered that in the context of a factual statement regarding the design of the TAX 326 study, the description of the treatment regimen of the Taxotere/carboplatin arm of the study in the leavepiece did not constitute promotion of an unlicensed combination. No breach of the Code was ruled.

COMPLAINT

Pierre Fabre alleged that the folder enclosing a copy of Fossella *et al* promoted the use of the unlicensed combination of Taxotere plus carboplatin in breach of Clause 3.2 of the Code. The company noted that it had been established that clinical papers as an integral part of promotional material and on exhibition stands should comply with the marketing authorization for a product.

RESPONSE

Aventis noted that Clause 3.2 of the Code stated 'The promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics'.

Aventis stated that Fossella *et al*, 'Randomised, Multinational, Phase III Study of Docetaxel Plus Platinum Combinations Versus Vinorelbine Plus Cisplatin for Advanced Non-Small-Cell Lung Cancer: The TAX 326 Study Group', was considered to be of significant clinical importance and was fast-tracked for publication by the Journal of Clinical Oncology in July 2003. This was a three-arm, multi-centre, randomised, controlled Phase III Study, recruiting more than 1,200 patients. The three arms were Taxotere/cisplatin, Taxotere/carboplatin and vinorelbine/cisplatin. On the basis of this study the combination of Taxotere/cisplatin was granted a licence by the Food and Drug Administration (FDA) in November 2002, and by the European Medicines Evaluation Agency (EMEA) in January 2003.

Aventis noted that oncology involved the use of a number of combinations of medicines at varying doses, both in clinical practice as well as within clinical trials. Many trials would contain an arm which might not subsequently be licensed, which was the case in Fossella *et al*. Nevertheless, the provision of information on the complete study, both the unsuccessful as well as the successful arm, was of scientific value to the prescriber. Aventis noted that Case AUTH/1483/6/03 was about a leavepiece in which a summary of the study design, including a description of all three arms, was presented. Aventis submitted that a verbal response from the Authority following the appeal by Aventis indicated that the Appeal Board agreed with Aventis that the use of Fossella *et al* was not inconsistent with the Taxotere SPC and was valid in providing balanced scientific information.

Aventis denied the allegation that the provision of Fossella *et al*, which had been in the public domain since July 2003, was in breach of Clause 3.2 of the Code. The company considered that to preclude the dissemination of important studies, such as this, would set a precedent that would be a disservice to the scientific community.

PANEL RULING

The Panel noted that when Aventis responded to this case, Case AUTH/1525/10/03, its appeal against the Panel's ruling of a breach of Clause 3.2 in Case AUTH/1483/6/03 had been heard although the company had not received written confirmation of the Appeal Board's ruling. In accordance with normal practice Aventis had been provided with limited information as to the outcome of the appeal by telephone which had been followed up by full written information. The Panel noted that in Case AUTH/1483/6/03 the Appeal Board had considered that, in the context of a factual statement regarding the design of the TAX 326 study, reference to the combination of Taxotere plus carboplatin did not constitute promotion of an unlicensed combination. The leavepiece was not inconsistent with the Taxotere SPC in that, as in the SPC, although the dosage and schedule details of the TAX 326 study were given, there was no reference to the outcome of treatment with Taxotere plus carboplatin. No breach of Clause 3.2 was ruled.

The Panel disagreed with Aventis' submission that in Case AUTH/1483/6/03 the Appeal Board had considered that the use of Fossella *et al* was not inconsistent with the Taxotere SPC and was valid in providing balanced scientific information. In the Panel's view the Appeal Board had ruled no breach of the Code due to the context in which the description of the study design from Fossella *et al* had been presented. It had been important to the Appeal Board's decision that no outcome data for the Taxotere/carboplatin arm had been included in the leavepiece.

The Panel considered that the folder, together with the copy of Fossella *et al*, provided more than the limited information given about the study in the leavepiece at issue in Case AUTH/1483/6/03. The copy of Fossella *et al* had been provided, unsolicited, in a promotional folder. The Panel noted that the supplementary information to Clause 11.1 of the Code, provision of reprints, stated that 'The provision of an unsolicited reprint of an article about a medicine constitutes promotion of that medicine and all relevant requirements of the Code must therefore be observed. Particular attention must be paid to the requirements of Clause 3'.

The Panel considered that the unsolicited provision of Fossella *et al* constituted promotion of the unlicensed combination of Taxotere plus carboplatin. A breach of Clause 3.2 was ruled.

APPEAL BY AVENTIS PHARMA

Aventis noted that Fossella *et al* was the only paper to report the findings of the pivotal registration study for the combination of Taxotere plus cisplatin which was licensed in the EU during January 2003. Taxotere was not licensed for combination chemotherapy with carboplatin.

The folder in question had been made available to specialist meetings, including a scientific meeting of the North Scotland Lung Cancer Group, and was designed to provide peer-reviewed scientific information to educated, highly trained and discerning specialists who were expert in the clinical management of lung cancer. This was not a piece for those with a casual interest in the area. Taxotere specialist oncology representatives carried it in order to provide the oncologists who wanted it, a copy of Fossella *et al*.

Aventis noted that in Case AUTH/1483/06/03 the Appeal Board ruled that the inclusion of an unlicensed treatment combination in the description of Fossella *et al* in a leavepiece had not constituted a breach of the Code. The Appeal Board ruling stated the following:

> 'Thus, the Appeal Board considered that in the context in which it appeared, i.e. a factual statement regarding the design of the Tax 326 study, the inclusion of the description of the treatment regimen of the Taxotere/carboplatin arm of the study in the leavepiece at issue did not constitute promotion of an unlicensed combination. The Appeal Board ruled no breach of Clause 3.2 of the Code'.

Aventis stated that in its view the nub of this case revolved around two notions. The first was an understanding of the difference between information and promotion. The second was set out in Clause 3.2 of the Code, namely:

> 'The promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in the summary of product characteristics' and the supplementary information to this clause: 'The promotion of indications not covered by the marketing authorization for a medicine is prohibited by this clause'.

Aventis submitted that the point at issue was that a piece did not have to be wholly consistent with the particulars in the SPC, but it must not be inconsistent. This permitted additional information to be present which was not inconsistent with the SPC rather than necessarily limiting a piece to only that which was consistent with the SPC.

Aventis submitted that it should not be restricted from going about its legitimate business, which included the promotion of the licensed indication for Taxotere in combination with cisplatin.

Aventis stated that European regulatory approval for Taxotere in combination with cisplatin was granted as a result of a single pivotal trial – TAX 326 (Fossella *et al*). Such regulatory practice was unusual. Granting regulatory approval on a small data package underpinned the fact that lung cancer had a poor prognosis and that there were reasonable grounds to expect benefit from Taxotere and cisplatin combination treatment in the right settings.

Aventis submitted that to actively withhold the knowledge that Taxotere and cisplatin could reasonably be expected to provide benefit to people with lung cancer, and not make it widely known to those people who had a responsibility to treat such patients, would be contradictory to accepted standards of morality and medical ethics. Aventis believed that the Appeal Board could never support the withholding of information in such circumstances.

Aventis noted that the Appeal Board had already confirmed that it was acceptable for the company to refer to Fossella *et al*, and it had also been ruled acceptable for it to provide a description of the study design in printed material designed to inform specialists about the licensed Taxotere and cisplatin treatment combination. By describing the study design in full it had therefore been confirmed as acceptable to include in the description of the study the second test arm, ie the unlicensed Taxotere/carboplatin combination. Thus it was established that it was not necessarily wrong to refer to an unlicensed treatment combination.

Aventis submitted that following the Appeal Board's ruling in Case AUTH/1483/6/03, it appeared acceptable to include limited reference to an unlicensed combination in a trial that had more than one test arm in its design when no promotional statements were made about the unlicensed combination and, importantly, the information was provided in order to give clarity to an issue about the data supporting the licensed indication that would otherwise be misleading if left out. Aventis stated that in this case it referred to the need to understand the requirement to use the Boneferroni correction method that was the subject of Case AUTH/1483/06/03.

Aventis recognised that considerable care had been taken by the authors of the Code to provide guidance on the important notions of accuracy, fairness, balance and presentation of scientific information. It was always preferable to provide people with sufficient, appropriately detailed information to let them make up their own minds. If this notion was accepted, it was not wrong to provide the most comprehensive peer-reviewed data available to specialists who were well versed in the critique and assessment of such comprehensive scientific papers. Moreover, as Fossella *et al* was the only data of this quality available it would be misleading not to include it in a document specifically directed at an expert audience. The folder in question was only made available to specialist audiences.

Aventis submitted that the issue could best be framed by the question: 'Must a scientific paper that is used to promote a treatment intervention only contain information that is within the licensed indications of the treatment or can it contain additional information that is not the subject of promotion?'.

Aventis understood the Panel's ruling only if an overly narrow view was taken of a clinical paper that referred to an unlicensed treatment; or suggested that an unlicensed treatment, dose or dosing interval etc, might provide benefit. It was important to draw the distinction between the provision of information and the promotion of a particular viewpoint. In the Oxford English Dictionary 'information' was defined as 'Communication of the knowledge of some fact or occurrence. Knowledge or facts communicated about a particular subject, event, etc, intelligence, news'. Whereas 'promotion' was defined as 'The publicization (sic) of a product; the advertisement of the merits of a commodity etc, an instance of this'. Nowhere in the folder had Aventis promoted an unlicensed indication for Taxotere, or promoted the limb in Fossella *et al* paper.

In summary Aventis submitted that it had legitimately promoted the value of the licensed combination of Taxotere and cisplatin by providing Fossella *et al* in an unsolicited manner. It had made no promotional reference to an unlicensed combination of Taxotere or carboplatin. The specialist audience to whom the folder was directed could discern which treatments had benefit and in which circumstances these benefits were likely to accrue.

Aventis submitted that there was a difference between providing information and promoting a viewpoint. The text box on the back cover of the re-print included by the publishers stated that 'The ideas and opinions expressed in this publication do not necessarily reflect those of the American Society of Oncology, or Adis'. This statement pointed out that making something available had not meant endorsement, let alone promotion of the ideas and thoughts included.

Aventis noted that there were many seminal papers for important therapeutic areas such as cancer, anti-infectives and cardiovascular medicine, that referred to unlicensed treatments, treatment schedules and doses. It would be a nonsense to restrict the distribution of seminal papers like Fossella *et al*, that were the only source of critical information upon which important decisions had to be made, simply because they contained more information than that contained in an SPC. This additional information should not be promoted and it had not done so. Information in scientific papers should not be censored, it should be available in its peer-reviewed, published form. Censoring was for the intelligent, informed reader to do after they had considered all of the information.

Aventis submitted that finally, if its appeal was unsuccessful, the consequence would be that many of the important notions embodied in the Medicines Act, and the Code, most notably balance, accuracy and format of presentation, would have to be flouted by many companies as they would always be expected to present data in a summarised form, rather than using original scientific text which was peer-reviewed and open to rigorous scientific critique. This approach could not be what the authors of the Code meant as they drafted the document.

COMMENTS FROM PIERRE FABRE

Pierre Fabre stated that this complaint related to the use of the Fossella *et al* paper as promotional material and the requirement of Aventis to comply with the Code. Aventis had suggested that it might be the only conduit through which physicians would have access to this information but the Journal of Clinical Oncology was popular and readily available to health professionals in every oncology unit or centre in the UK and available online and through Medline. Pierre Fabre alleged that any assertions that this case would limit a scientific discussion or 'would be acting in a manner contradictory to accepted standards of morality and medical ethics' were misplaced. In fact, there was already an increasing debate in the UK regarding both the dose of cisplatin used in the control arm and major errors in the methodology of the quality of life measurement presented in this study that could potentially bias the results.

Pierre Fabre noted that the EMEA had granted a marketing authorization for Taxotere plus cisplatin in January 2003. However, neither the EMEA nor any other regulatory body in the world had granted a marketing authorization for Taxotere plus carboplatin.

Pierre Fabre noted that reference to the carboplatin combination was made Section 5.1, Pharmacodynamic properties, of the European SPC to identify the design of the TAX 326 study. Pierre Fabre noted that neither the EMEA nor the FDA had included any reference to the results or toxicity of the carboplatin arm in the UK, European or American SPCs. Reference to the carboplatin arm in Section 5.1 had not constituted a marketing authorization for the Taxotere/carboplatin combination, a fact accepted by Aventis in Case AUTH/1483/6/03.

Pierre Fabre was disturbed by the number of Aventis' current promotional items in which the unlicensed arm of this study was being used as a promotional platform for Taxotere plus carboplatin. In addition to this current case, further UK promotional material referring to the Taxotere/carboplatin arm had already, upon request, been withdrawn by Aventis without reference to the Authority, and some 'international material' collected at a meeting in the UK that included a video CD in which the details of the unlicensed arm were described as fully as by Fossella *et al*.

Pierre Fabre alleged that the Fossella *et al* reprint was an integral part of the folder and therefore constituted promotion of that medicine as described under Clause 11.1 and must comply with the Code. This material, including the reprint, must therefore be fully consistent with the marketing authorization for Taxotere. The marketing authorization for Taxotere was described in Section 4.1, Therapeutic Indications, of the SPC:

> 'Taxotere (docetaxel) is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.
>
> Taxotere in combination **with cisplatin** (emphasis added) is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition'.

Pierre Fabre alleged that the provision of extensive clinical detail of Taxotere plus carboplatin in the folder in question was inconsistent with the marketing authorization for Taxotere.

Pierre Fabre alleged in summary that it was clear that the inclusion of an unsolicited clinical reprint within the folder constituted promotion and must comply with Clause 3.2 of the Code. There was no marketing authorization for Taxotere plus carboplatin and therefore this material was in breach of Clause 3.2.

APPEAL BOARD RULING

The Appeal Board considered that Fossella *et al* was an integral part of the folder and that the unsolicited provision of the paper constituted promotion of the unlicensed combination of Taxotere plus carboplatin as alleged. In this regard the Appeal Board noted the supplementary information to Clause 11.1 of the Code that the provision of an unsolicited reprint of an article about a medicine constituted promotion of that medicine and all relevant requirements of the Code must therefore be observed. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2 of the Code. The appeal was unsuccessful.

Complaint received **7 October 2003**

Case completed **2 February 2004**

CASE AUTH/1527/10/03

GLAXOSMITHKLINE v ASTRAZENECA

e-mail relating to the SUND study

GlaxoSmithKline complained about an unsolicited email sent to UK health professionals registered on the AZ-AIR website operated by the global part of the AstraZeneca organisation. The email directed prescribers to data from the Symbicort Up aNd Down (SUND) study and indirectly to a press release. The SUND study compared fixed and adjustable dosing regimens of AstraZeneca's product Symbicort with a fixed dose of GlaxoSmithKline's product Seretide. GlaxoSmithKline considered that the study did not compare like with like and noted that the maximum allowable dose of Symbicort (up to 8 inhalations a day) in the adjustable dosing arm of the study was double that currently licensed in the UK. Additionally the study failed to demonstrate a statistical difference in the primary composite endpoint of asthma control and it was important that the significance of secondary endpoints were viewed in this context.

GlaxoSmithKline considered that the email came within the scope of the Code. A person's country of origin data was collected when they registered on AZ-AIR and so AstraZeneca would know that the email was going to UK doctors; such communication was the responsibility of the UK company. The email made a superiority claim for adjustable Symbicort vs fixed Seretide linked to data from the SUND study. GlaxoSmithKline alleged that the email promoted Symbicort but noted that there was no link to the prescribing information. GlaxoSmithKline further alleged that the email, which referred to unlicensed data which had been reported in an unbalanced and misleading way, was in breach of Clause 2 of the Code.

The Panel noted that the email, dated 12 September and sent on 14 September, referred to the European Respiratory Society congress to be held in Vienna. It included an invitation to two evening symposia. It also listed four items of medical news including 'Astra says asthma drug beats Glaxo rival in test'. Symbicort was not mentioned by name in the email. A link was provided to 'Medical News'. The link supplied with the email detailed 22 news items 'On AZ-AIR this week' September 9-14 2003. The news item 'Astra says asthma drug beats Glaxo rival in test' referred to Symbicort. The report stated that the rate of severe exacerbations in asthma patients was 40% lower among those taking adjustable doses of Symbicort than in patients on fixed doses of Seretide.

The Panel noted AstraZeneca's submission that the email was sent to individuals registered on www.az-air.com, which was limited to health professionals who had registered on line, and that emails were only sent to those who wished to receive them. The Panel noted however that although the registration box included an option to receive the AZ-AIR newsletter, it appeared that one of the obligatory terms of registration was that AstraZeneca would send emails and provide its weekly newsletter. Thus despite the appearance of choice there was none. AstraZeneca stated that the 'Medical News' link was an independently generated business news story from Reuters which was reproduced on the website. The Panel noted that it was possible to register on www.az-air.com other than as a health professional.

The Panel noted that the email did not mention Symbicort but the linked article did; the two had to be considered together. The Panel considered that the email and the linked article promoted advantages for Symbicort compared with Seretide. The Panel considered that prescribing information and a statement as to where such information could be found were required and as they had not been provided breaches of the Code was ruled in respect of both the email and linked article. The email and the linked Internet article both included dates which the Panel considered were sufficient to comply with the requirement for including the date on which the material was drawn up or last revised. No breach of the Code was ruled in that regard. The material had not been certified as required by the Code and a breach was ruled.

The Panel noted that it appeared that the recipients in registering on the website had no choice other than to agree to receive emails. The Panel did not consider that an obligatory agreement of this kind demonstrated that permission had been given to receive promotional material; the Panel had no option but to rule a breach of the Code.

The Panel noted AstraZeneca's submission that the email had been sent to health professionals only. There was no evidence that the email had been sent to the public. The Panel thus decided to rule no breach of the Code in that regard. The SUND study results were on doses outside the UK marketing authorization. The Panel thus ruled a breach of the Code as the email and linked article were not in accordance with the terms of the marketing authorization. The description of the outcome of the study was limited and did not put the results within the overall context of the study. No mention was made of the fact that no difference was shown in relation to the odds of achieving a well-controlled asthma week. The Panel considered that the email and linked article constituted a misleading comparison which was not capable of substantiation. Breaches of the Code were ruled.

The Panel noted that Clause 2 was used as a sign of particular censure and decided that the circumstances did not warrant a ruling of a breach of Clause 2 of the Code.

GlaxoSmithKline UK Ltd complained about promotional activity by AstraZeneca UK Limited in relation to the SUND (Symbicort Up aNd Down) study which it had sponsored. The material at issue was an email. AstraZeneca marketed Symbicort (eformoterol/budesonide). GlaxoSmithKline marketed Seretide (salmeterol/fluticasone). Dialogue between the companies had failed to resolve the issues.

COMPLAINT

GlaxoSmithKline stated that abstracts from the SUND study were first presented on 7 September 2003 at the World Allergy Organisation's International Congress of Allergology and Clinical Immunology (ICACI).

GlaxoSmithKline had serious concerns over a claim of 'superiority' for Symbicort vs Seretide made in relation to the SUND study. Firstly, with regard to the study design, GlaxoSmithKline noted that the doses of Symbicort (up to 8 inhalations a day) used in the adjustable dosing arm of the SUND study far exceeded those licensed in the UK (up to 4 inhalations). GlaxoSmithKline alleged that this was inconsistent with the summary of product characteristics (SPC) in breach of Clause 3.2.

Further, in GlaxoSmithKline's view the study design was not robust and prevented a superiority claim being made. Patients entered the study and after a run-in period on existing treatment were randomised to one of two double-blind groups on fixed dose treatment regimens with either Seretide or Symbicort. After 4 weeks the patients were then divided into 4 open label groups: Seretide fixed dose, Symbicort fixed dose, and two Symbicort flexible dosing groups. These groups were studied over a further six months. The superiority claim was based on an open-label study. It compared two treatment regimens ie fixed and adjustable dosing and not two medicines in an open-label design. To enable a true comparison the study would have required a Seretide adjustable dosing regimen. In summary this was a weak trial design where like had not been compared with like and any superiority claim was scientifically unsound.

With regard to the statistical analysis of the SUND study GlaxoSmithKline stated that although it had not been able to view the full data set, the primary endpoint was defined as the odds of achieving a well-controlled asthma week. This was a composite measure of asthma control, which included, *inter alia*, asthma exacerbations. The study showed that there was no statistical significance in this endpoint between any of the arms of the study. Despite this, superiority claims had been made on the primary endpoint of control and the secondary endpoint of exacerbations reporting a 40% lower rate of severe exacerbations among those taking adjustable doses of Symbicort than in patients on fixed doses of Seretide. It was of note that no statistical analysis had been provided for this claim. Furthermore, it was not surprising that patients on Seretide had a greater number of exacerbations compared to the Symbicort adjustable dose regimen, as unlike in true clinical practice, no intervention was permitted.

In summary GlaxoSmithKline alleged that the superiority claim was misleading because: the fundamental study design was not robust and did not compare like with like under controlled conditions; the primary endpoint failed to meet statistical significance and because of this the significance of the secondary endpoint could not be accurately assessed by the reader unless explanation was given to the shared significance of multiple endpoint in the absence of a non-significant primary endpoint.

GlaxoSmithKline had carefully reviewed the published abstracts relating to this study and had concerns about the consequent claims made, believing them to be inaccurate, unbalanced and misleading. The SUND study included doses and protocols outside the UK marketing authorization for Symbicort.

GlaxoSmithKline noted that UK medical practitioners registered with AstraZeneca's AZ-AIR website received an unsolicited email during October 2003 that directed them to data from the SUND study and indirectly to a press release. GlaxoSmithKline had grave concerns with both the nature and content of the email. The company considered that the email fell within the scope of the Code since country of origin information was collected, when registering with AZ-AIR. Therefore AstraZeneca knew that it was communicating with UK practitioners. Any communication between AstraZeneca and doctors in the UK was the responsibility of the UK company and communications should go through the usual approval process prior to dissemination.

The email was received by one of GlaxoSmithKline's medical staff, who was a respiratory physician, registered with AZ-AIR, on 12 September 2003. This email was unsolicited and not in response to a specific enquiry. The AZ-AIR website could be accessed by any member of the public, but on registering they were asked for details of geographical location.

The email contained a statement under Medical News: 'Astra says asthma drug beats Glaxo rival in test' and invited the reader to click on a link to find out more. The link took the reader to the Medical News page of the AZ-AIR website where the article 'Astra says asthma drug beats Glaxo rival in test' was detailed.

The email made a superiority claim, which was vaguely and not precisely referenced to the SUND study, but linked directly to data emanating from it. However there was enough information contained in the news article to understand this fact without the item being appropriately referenced.

The email was clearly promotional and directly linked to an article which mentioned Symbicort by name. The email made a superiority claim, had been sent unsolicited to UK doctors and was linked to an article which did not contain prescribing information, nor was it clear where this might be found. GlaxoSmithKline therefore alleged that the email was in breach of Clause 9.9, and the linked Internet article in breach of Clauses 4.1, 4.3, 4.6, 4.9 and 14.1.

GlaxoSmithKline alleged that unsolicited emails drawing UK practitioners' attention to out of licence data, which had been reported in an unbalanced and misleading way, constituted promotional activity and as such was in breach of Clause 2.

RESPONSE

AstraZeneca did not consider that the email was within the scope of the Code. The activity related to an international website over which the AstraZeneca UK marketing company had no control or responsibility.

AstraZeneca explained that the linked news story 'Astra says asthma drug beats Glaxo rival in test' was one item in a respiratory news feed written by Reuters and was unedited and unfiltered by AstraZeneca. Although the intended audience of the site was medical, Reuters' story actually had a business orientation. Az-air.com (AZ-AIR) was a global site that was not based within or run by the AstraZeneca UK marketing company. It was hosted on a server in Sweden and operated by global parts of the AstraZeneca organisation. AstraZeneca had separate UK websites for UK citizens eg www.astrazeneca.co.uk and the material at issue was not carried on AstraZeneca's UK websites. UK journalists constituted one of many nationalities that obtained information from AstraZeneca's global sites but there was no activity directed specifically at UK journalists. AstraZeneca's global websites were reviewed opposite global codes and rules including the IFPMA Code of Pharmaceutical Marketing Practices.

AstraZeneca stated that AZ-AIR was meant for health professionals around the world and required registration, log in and password access. The UK marketing company had no influence on the content of this mainly educational and scientific site. During registration the country of origin for the reader was recorded, as was the case on numerous global websites, and this information was used for market research purposes. The proportion of UK registered users was below 10%.

AZ-AIR was an international website and was the responsibility of the global AstraZeneca respiratory business in Sweden. The information was placed on the Internet by global business communication staff, through a server in Sweden, without the authority or involvement of the AstraZeneca UK marketing company. Further, Clause 21.2 required that the material made specific reference to availability or use in the UK – the material made no such reference. It was not directed at a UK audience. Based on these criteria AstraZeneca submitted that AZ-AIR was not subject to the Code.

With regard to the email AstraZeneca's understanding of the Code was that there was no clause that necessitated the specific requirements of the Code (eg in relation to emails) to be applied to non-UK websites. There were numerous international websites, and also websites subject to American and other national regulations, which had UK subscribers and many of these sites sent regular alerting emails to worldwide recipients. It was simply not practical for these emails to be reviewed by national signatories in all the countries to which they went (including the UK) and/or to be subject to all the different and inconsistent national regulations in dozens of countries. AstraZeneca believed that it was never intended that the Code should impose unworkable restrictions with respect to global email communications. As stated above, however, AstraZeneca's global websites were reviewed opposite global codes and rules including the IFPMA Code.

In conclusion AstraZeneca submitted that the contents of www.az-air.com should not come under the remit of the UK Code. A ruling on this principle had wide implications for global and overseas-based pharmaceutical company websites, potentially seriously inhibiting the use of the Internet for legitimate and proper communications worldwide.

AstraZeneca explained that combination therapies containing inhaled steroids and long-acting beta-agonists were widely used within current asthma management. There were distinct pharmacological differences between Symbicort (eformoterol/budesonide) and Seretide (salmeterol/fluticasone) the most significant of these being the clinically proven dose response of eformoterol over a wide dose range compared to negligible dose response over a very narrow dose range for salmeterol. A much faster onset of action (similar to that of the traditional fast acting beta-agonists) was another distinct feature of eformoterol compared with salmeterol. These differences meant that Symbicort could be used in an adjustable fashion as well as the conventional fixed dose maintenance therapy. Indeed clinical studies comparing the efficacy of adjustable maintenance therapy and fixed dose therapy with Symbicort had shown adjustable therapy to be at least as effective as fixed dose therapy but at a lower overall drug load. Following on from these assumptions and clinical data, the question being asked in UK practice was 'Symbicort can be used as fixed and adjustable dosing whereas Seretide can only be used as fixed dosing. Symbicort adjustable dosing compares well with fixed dosing. How does it compare with the other combination therapeutic option – Seretide fixed dosing?' The SUND study had been designed to answer this valid clinical question that was important to prescribers.

In the SUND study the three treatment arms after randomisation were Symbicort 200/6 two inhalations twice daily (fixed dose), Seretide 250/50 one inhalation twice daily (fixed dose) and Symbicort 200/6 adjustable maintenance dose. The current Symbicort UK licence allowed for adjustable treatment: 1-2 inhalations twice daily; when control of symptoms was achieved with twice daily Symbicort, titration to the lowest effective dose could include Symbicort given once daily. The study design allowed patients in the Symbicort adjustable treatment arm to increase their dose of Symbicort to 4 inhalations twice daily for short periods. This higher dose was currently not licensed in the UK although an application for a variation in the licence allowing such a dose had been submitted and AstraZeneca was awaiting a decision on this application.

In the light of this, and to ensure compliance with the Code, AstraZeneca UK had briefed its sales teams not to promote any of the data or messages from the SUND study. Details of the SUND study were not included in any promotional materials or activities. There had been no public relations activities around the SUND data from the AstraZeneca UK marketing company and the content of the website in question had had no AstraZeneca UK input.

In response to specific alleged breaches related to the email AstraZeneca noted that emails were only sent to individuals registered on the AZ-AIR website. This site was only for health professionals who had gone

through registration online. Email alerts were only sent to those who identified that they wished to receive them. The emails were not unsolicited. The email at issue was one of a regular series of alerting emails that drew attention to recent stories; it included a headline taken from an independently generated business news story from Reuters which was reproduced on the AZ-AIR website. These respiratory news stories were written by Reuters and were unedited and unfiltered by AstraZeneca – past stories included examples of positive news for other companies' products. AstraZeneca submitted that the email in itself could not be considered promotional. It included a number of headlines and other information. It did not mention Symbicort by name – the 'asthma drug' mentioned in one headline could be any of several. AstraZeneca considered that the email therefore did not require prescribing information to be provided and did not require certification under the Code. Additional information on the SUND study had appeared on the AZ-AIR website. The information could be found after several clicks in a section on adjustable maintenance dose. The presentation was sufficiently informative and comprehensive as a presentation of adjustable maintenance therapy, to be considered as non-promotional.

In summary, AstraZeneca submitted that the content of the email to health professionals who were already registered with the website was non-promotional and therefore not a breach of Clauses 9.9, 4.1, 4.3, 4.6, 4.9 and 14.1.

Finally, AstraZeneca stated that it considered that drawing attention of UK (and non-UK) practitioners to a website with which they were already registered, where that website contained clinically important data as part of a scientific presentation, could not and did not bring the pharmaceutical industry into disrepute. It was vital that pharmaceutical companies made every effort to inform practitioners of the latest clinical and pharmaceutical developments. AstraZeneca therefore denied any breach of Clause 2.

Summary

- All the activities related an international website over which the UK operational unit of AstraZeneca had no control or responsibility. AstraZeneca did not believe that the email fell within the remit of the Code.
- The information given on the website was clear and unambiguous. It did not misrepresent primary and secondary endpoints and provided a balanced account of the study.
- The information was not promotional or misleading. It was not promoting outside of the current licence.
- The SUND study sought to answer a clinically important question and was of robust design.
- AstraZeneca UK was aware of the differences between the current UK licence and the adjustable dosing arm in the SUND study. As such it had actively ensured compliance with the UK Code. The distributions of both briefings were appropriate and non-promotional. AstraZeneca UK was not engaged in any PR activity around these briefings.
- The email sent to previously registered health professionals relating to a scientific and clinical presentation (of which the SUND study was a part) was non-promotional.

AstraZeneca therefore denied all alleged breaches.

PANEL RULING

The Panel considered that it first had to decide whether the email was subject to the Code. The supplementary information to Clause 3, Marketing Authorization stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided any such information or activity did not constitute promotion which was prohibited under that clause or any other clause.

Clause 21.2 of the Code stated that information or promotional material about medicines covered by Clause 21.1 (ie those that could not legally be advertised to the general public) which was placed on the Internet outside the UK would be regarded as coming within the scope of the Code if it was placed there by a UK company or an affiliate of a UK company or at the instigation or with the authority of such a company and it made specific reference to the availability or use of the medicine in the UK. The Panel did not accept AstraZeneca's submission that for material to fall under Clause 21.2 there was a requirement for both the involvement of the UK company and the material to make reference to availability or use in the UK. That was not so. If such material had been placed on the website by an affiliate of a UK company without the knowledge or involvement of the UK company it could, nonetheless, be caught by Clause 21.2 and thus come within the scope of the Code.

The Panel noted that the email dated 12 September and sent on 14 September referred to the European Respiratory Society congress to be held in Vienna. It included an invitation to two evening symposia. It also listed four items of medical news including 'Astra says asthma drug beats Glaxo rival in test'. Symbicort was not mentioned by name in the email. A link was provided to 'Medical News'. The link supplied with the email detailed 22 news items 'On AZ-AIR this week' September 9-14 2003. The news item 'Astra says asthma drug beats Glaxo rival in test' referred to Symbicort. The report stated that the rate of severe exacerbations in asthma patients was 40% lower among those taking adjustable doses of Symbicort than in patients on fixed doses of Seretide.

The Panel noted AstraZeneca's submission that the email was sent to individuals registered on www.az-air.com, which was limited to health professionals who had registered on line, and that emails were only sent to those who wished to receive them. The Panel noted however that although the registration box included an option to receive the AZ-AIR newsletter it appeared that one of the obligatory terms of registration was that AstraZeneca would send emails

and provide its weekly newsletter. Thus despite the appearance of choice there was none. AstraZeneca stated that the 'Medical News' link was an independently generated business news story from Reuters which was reproduced on the website.

The Panel noted that replies in response to individual enquiries from health professionals were not included in the definition of promotion if they related solely to the subject matter of the letter or enquiry, were accurate, did not mislead and were not promotional in nature (Clause 1.2 of the Code). Given the obligatory terms of registration it appeared that the email at issue had not been sent in response to an individual enquiry and thus could not take the benefit of this exemption to the Code. In the Panel's view the email was thus subject to the Code.

The Panel noted that it was possible to register on www.az-air.com other than as a health professional.

The Panel noted that the email did not mention Symbicort but the linked article did; the two had to be considered together.

The Panel considered that the email and the linked article promoted advantages for Symbicort compared with Seretide. The Panel considered that prescribing information was required and as it had not been provided a breach of Clause 4.1 of the Code was ruled in respect of both the email and linked article.

The material did not include a clear prominent statement as to where the prescribing information could be found as required by Clause 4.6 of the Code and a breach was thus ruled. The email and the linked Internet article both included dates which the Panel considered were sufficient to comply with the requirement for including the date on which the material was drawn up or last revised. No breach of Clause 4.9 of the Code was ruled.

The material had not been certified as required by Clause 14.1 and a breach of that clause was ruled.

Clause 9.9 required that promotional material should not be sent by email without the prior permission of the recipient. It appeared that the recipients in registering on the website had no choice other than to agree to receive emails. The Panel did not consider that an obligatory agreement of this kind demonstrated that permission had been given to receive promotional material; the Panel had no option but to rule a breach of Clause 9.9.

The Panel noted that GlaxoSmithKline had alleged that the use of the data from the SUND study breached Clauses 3.2, 7.2, 7.3, 7.4 and 20.2 of the Code. The Panel considered that as the email and linked article referred to the SUND study it was obliged to consider the clauses cited by GlaxoSmithKline.

The Panel noted AstraZeneca's submission that the email had been sent to health professionals only. There was no evidence that the email had been sent to the public. The Panel thus decided to rule no breach of Clause 20.2 which related to information provided to the general public. The SUND study results were on doses outside the UK marketing authorization. The Panel thus ruled a breach of Clause 3.2 of the Code as the email and linked article were not in accordance with the terms of the marketing authorization. The description of the outcome of the study was limited and did not put the results within the overall context of the study. No mention was made of the fact that no difference was shown in relation to the odds of achieving a well-controlled asthma week. The Panel considered that the email and linked article constituted a misleading comparison which was not capable of substantiation. Breaches of Clauses 7.2, 7.3 and 7.4 of the Code were ruled.

The Panel noted that Clause 2 was used as a sign of particular censure and decided that the circumstances did not warrant a ruling of a breach of Clause 2 of the Code.

Complaint received **13 October 2003**

Case completed **6 February 2004**

CASE AUTH/1533/10/03

SERVIER v TAKEDA

Actos journal advertisement

Servier complained about a journal advertisement for Actos (pioglitazone) issued by Takeda. Actos could be used alone particularly in overweight type 2 diabetics who were inadequately controlled by diet and exercise but who could not take metformin. Actos could also be used in combination in patients with insufficient glycaemic control despite maximal tolerated doses of either metformin or a sulphonylurea; in combination with metformin particularly in overweight patients and in combination with a sulphonylurea in patients who could not take metformin. Servier marketed Diamicron (gliclazide) a sulphonylurea.

Servier noted that the claim 'Actos can now be used as monotherapy' appeared beneath the main claim 'Is it time to say Move over Sulphonylurea?'. Servier further noted that although Actos was licensed for use in monotherapy, such use was restricted to patients in whom metformin was not suitable. There was no such qualification within the body of the advertisement. The statement 'Now, when metformin isn't suitable, you can prescribe Actos instead of a sulphonylurea as monotherapy' appeared in much smaller text below the main body of the advertisement and could not be considered adequate qualification of the headline claim.

The Panel noted that metformin was the medicine of first choice in overweight patients in whom strict dieting had failed to control their diabetes (ref British National Formulary, September 2003). Actos was now licensed for use in these patients and others although particularly for those who were overweight, for whom metformin was not an option due to contraindications or intolerance. Such patients in the past might have been prescribed a sulphonylurea. In the Panel's view the patient group in whom Actos could be used as monotherapy was not adequately described in the advertisement. The question 'Is it time to say Move over Sulphonylurea?' followed by the claim at issue was ambiguous. As well as applying to the patient group for whom Actos monotherapy was licensed it could also be read to mean that Actos could be given as monotherapy to any patient who would otherwise have been given a sulphonylurea. This was not so. Although the statement 'Now, when metformin isn't suitable, you can prescribe Actos …' appeared in the main body of text at the bottom of the advertisement, this was not sufficiently prominent to ensure that prescribers would know the patient group for whom Actos could be used as monotherapy. The Panel thus considered that, within the context of the advertisement, the claim 'Actos can now be used as monotherapy' was misleading about the licensed indication of Actos as monotherapy; a breach of the Code was ruled.

Servier alleged that the headline 'Is it time to say Move over Sulphonylurea?' was misleading because, despite the question mark, which was partially obscured by a figure carrying a banner 'Perky Pancreas', the impression of the advertisement was that Actos could be used without restriction, as an alternative to a sulphonylurea. This impression was not consistent with the licensed indications for Actos, or in line with accepted medical practice.

Sulphonylureas could be used as a first-line pharmacological treatment of type 2 diabetes, without restriction whereas Actos, both in monotherapy and in combination, should only be used when alternative options were inappropriate. Actos monotherapy was also further implicitly restricted by the emphasis on its usage in overweight patients. Servier alleged that the overall impression of the advertisement was misleading in terms of the licensed indications and common medical practice.

The Panel noted its comments above about the place of Actos monotherapy and the overall impression created by the advertisement and considered that, in the context in which it appeared, the statement 'Is it time to say Move over Sulphonylurea?', was misleading about the licensed indication of Actos as monotherapy. The description of Actos in the main body of text as an 'excellent alternative to a sulphonylurea' compounded the overall impression given. The Panel further considered that in the context in which it appeared the statement was inconsistent with the marketing authorization for Actos. Breaches of the Code were ruled.

Servier alleged that the term 'Perky Pancreas' was exaggerated. While the term 'perky' was highly subjective the average reader would consider it meant 'lively', functioning above expected parameters, or outperforming relative to the norm. ß-cell function was considered a good indicator of diabetic pancreatic function. It had been shown that in type 2 diabetes, ß-cell function had already declined before diagnosis and continued to decline in patients who were treated initially by diet. Servier contended that by the time a patient was taking Actos, there was already likely to be significant pancreatic dysfunction. Although the Actos summary of product characteristics (SPC) stated 'HOMA analysis shows that pioglitazone improves beta cell function as well as increasing insulin sensitivity. One year clinical studies have indicated maintenance of this effect', Servier contended that such results needed to be placed in the context of the condition of the pancreas at the start of therapy, as stated above. Furthermore Servier noted that in a large prospective study type 2 diabetics treated with diet, sulphonylurea or metformin all showed improved ß-cell function after one year before a decline over the following five. Servier thus questioned the use of one year data to justify the term 'Perky Pancreas' and its implied superiority to sulphonylureas in the phrase 'Move over Sulphonylurea'.

Finally, Servier alleged that the use of a study (Hanefield and Göke, 2000), which focused on the role of Actos in combination with other oral antihyperglycaemic agents, to support a claim in a misleading advertisement for the use of Actos in monotherapy was invalid.

Regardless of the strength of these data, Servier considered that the pancreas of a type 2 diabetic

could not by any definition be described as 'perky' in the sense that this would be viewed by the average reader.

The Panel noted the intended audience and Takeda's submission that the average reader would expect a type 2 diabetic to have a dysfunctional pancreas. The phrase 'Perky Pancreas' implied that such a pancreas would improve with treatment. The Panel did not consider that the phrase 'Perky Pancreas' exaggerated the effect of Actos upon the pancreas nor did it imply superiority to sulphonylureas as alleged. No breach of the Code was ruled in both regards.

Servier Laboratories Ltd complained about a journal advertisement (ref AC030401a) for Actos (pioglitazone) issued by Takeda UK Limited.

Actos was indicated as oral monotherapy in type 2 diabetes mellitus, particularly in overweight patients, inadequately controlled by diet and exercise for whom metformin was inappropriate because of contraindications or intolerance. Actos was also indicated for combination treatment in type 2 diabetics with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea: in combination with metformin particularly in overweight patients, in combination with a sulphonylurea only in patients intolerant to metformin or for whom metformin was contraindicated.

Servier marketed Diamicron (gliclazide) a sulphonylurea indicated for the treatment of type 2 diabetes.

1 Claim 'Actos can now be used as monotherapy'

This claim appeared beneath the main claim 'Is it time to say Move over Sulphonylurea?'.

COMPLAINT

Servier noted that Section 4.1 of the Actos summary of product characteristics (SPC) stated 'Pioglitazone is indicated as oral monotherapy in type 2 diabetes mellitus patients, particularly overweight patients, inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance'. Thus Actos monotherapy was restricted to patients for whom metformin was unsuitable. There was no such qualification within the body of the advertisement. Although the statement 'Now, when metformin isn't suitable, you can prescribe Actos instead of a sulphonylurea as monotherapy', appeared in much smaller text below the main body of the advertisement this was functionally a footnote and therefore could not be considered adequate qualification of the headline claim. As stated in the supplementary information to Clause 7, 'In general claims should not be qualified by the use of footnotes and the like'. Servier alleged that the advertisement promoted the use of Actos in monotherapy without qualification, and that it therefore misled as to the licensed indications for Actos in breach of Clause 7.2.

Servier considered that the advertisement at issue was similarly misleading with regard to licensed indications to those at issue in two previous cases, Case AUTH/1084/10/00 and Case AUTH/1169/3/01.

RESPONSE

Takeda explained that the advertisement told prescribers that Actos could now be used in monotherapy, reflecting the recent change to the licence. This announcement was made in the main body of the advertisement and continued in the first line of the copy. The copy itself was not, nor was it intended to be, a footnote, but was an integral part of the advertisement, which was why it was large enough for health professionals to clearly see and read, following on from the visual.

Takeda noted that the Actos SPC, Section 4.1 'Therapeutic indications' read: 'Pioglitazone is indicated as oral monotherapy in type 2 diabetes mellitus patients, particularly overweight patients, inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance'. Actos was thus indicated in patients with type 2 diabetes, who were inadequately controlled despite diet and exercise and were either intolerant or contraindicated to taking metformin. For a newly diagnosed type 2 diabetic patient, metformin was the most commonly prescribed oral medicine. Actos monotherapy could therefore be prescribed as an alternative to sulphonylureas should metformin not be suitable. The advertisement clearly went on to clarify and explain this positioning by stating: 'Now, when metformin isn't suitable, you can prescribe Actos instead of a sulphonylurea as monotherapy'.

For these reasons, Takeda submitted that the claim at issue was accurate and fair, and not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the advertisement read 'Is it time to say Move over Sulphonylurea? Actos can now be used as monotherapy'. Text at the bottom of the advertisement began 'Now, when metformin isn't suitable, you can prescribe Actos instead of a sulphonylurea as monotherapy.' and concluded 'So perhaps you'll agree: Actos is an excellent alternative to a sulphonylurea – either with or without metformin'.

The Panel noted that metformin was the medicine of first choice in overweight patients in whom strict dieting had failed to control their diabetes (ref British National Formulary No 46, September 2003). Actos was now licensed for use in these patients and others although particularly for those who were overweight, for whom metformin was not an option due to contraindications or intolerance. Such patients in the past might have been prescribed a sulphonylurea. In the Panel's view the patient group in whom Actos could be used as monotherapy was not adequately described in the advertisement. The question 'Is it time to say Move over Sulphonylurea?' followed by

the claim at issue was ambiguous. As well as applying to the patient group for whom Actos monotherapy was licensed it could also be read to mean that Actos could be given as monotherapy to any patient who would otherwise have been given a sulphonylurea. This was not so. Although the statement 'Now, when metformin isn't suitable, you can prescribe Actos …' appeared in the main body of text at the bottom of the advertisement this was not sufficiently prominent to ensure that prescribers would know the patient group for whom Actos could be used as monotherapy. The Panel thus considered that, within the context of the advertisement, the claim 'Actos can now be used as monotherapy' was misleading about the licensed indication of Actos as monotherapy; a breach of Clause 7.2 was ruled.

2 Claim 'Is it time to say Move over Sulphonylurea?'

COMPLAINT

Servier alleged that this headline was misleading because, despite the question mark, which was partially obscured by a figure carrying a banner 'Perky Pancreas', the advertisement implied that Actos could be used without restriction, as an alternative to a sulphonylurea. This was not consistent with the licensed indications for Actos, or in line with accepted medical practice.

Actos was indicated for monotherapy and for combination treatment; Servier referred to Section 4.1 of the Actos SPC. In contrast, the SPC indications for the sulphonylureas were 'Non insulin dependent diabetes mellitus' (Diamicron); 'Non insulin dependent diabetes (type 2) in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose' (Diamicron 30mg MR) and 'As an adjunct to diet, in non-insulin-dependent diabetics (NIDDM), when proper dietary management alone has failed' (Minodiab (glipizide)).

Thus it was clear that whereas sulphonylureas were appropriate as a first-line pharmacological treatment of type 2 diabetes, without restriction, Actos, both in monotherapy and in combination, should only be used when alternative options were inappropriate. Actos monotherapy was also further implicitly restricted by the emphasis in its SPC on usage in overweight patients. Servier alleged that these points were in direct contradiction to the tenor of the advertisement.

Servier noted that the NICE guidance on the use of glitazones for the treatment of type 2 diabetes (Technology Appraisal 63, August 2003) was a reflection of good and current medical practice. The first statement in this guidance was 'For people with type 2 diabetes, the use of a glitazone as second-line therapy added to either metformin or a sulphonylurea – as an alternative to treatment with a combination of metformin and a sulphonylurea – was not recommended except for those who were unable to take metformin and a sulphonylurea in combination because of intolerance or a contraindication to one of the drugs. In this instance, the glitazone should replace in the combination the drug that was poorly tolerated or contraindicated'. Whilst it was only fair to state that this guidance did not consider glitazones in monotherapy due to the absence of this indication at the time of publication, Servier considered that this gave strong evidence of the place of Actos in the pharmacological management of type 2 diabetes, namely that it should be considered a second-line agent.

Servier concluded that the overall impression of the advertisement, that Actos could be used as an unrestricted substitute for a sulphonylurea, either in monotherapy or in combination therapy, was both misleading in terms of the licensed indications and in terms of common medical practice, and therefore in breach of Clauses 3.2 and 7.2.

RESPONSE

Takeda stated that the question 'Is it time to say Move over Sulphonylurea?' served to ask prescribers to consider their current prescribing habits. For a newly diagnosed type 2 diabetic, metformin was the most commonly prescribed medicine. Hence when metformin was not suitable the prescriber now had two options where there had previously only been one ie to use a sulphonylurea. The question therefore asked whether it was time for the sulphonylureas to move over and make room for another option in the treatment of these patients. It was not a statement but purely a question to encourage prescribers to think about each patient they saw who was not suitable for metformin and decide whether to use a sulphonylurea or Actos.

Takeda stated that its comments at point 1 above also applied here in that Actos was indicated in patients with type 2 diabetes, particularly overweight patients, inadequately controlled despite diet and exercise and who were either intolerant or contraindicated to taking metformin. Actos was therefore an alternative monotherapy to sulphonylureas, which could be prescribed should metformin not be suitable.

Takeda stated that Servier had implied, incorrectly, that Actos monotherapy was restricted to overweight patients; the SPC stated 'particularly' overweight patients. The Oxford dictionary definition of 'particularly' in this context was 'used to single out a subject to which a statement is especially applicable'. In other words the SPC could be interpreted as 'especially' in overweight patients. It clearly did not mean only in overweight patients (emphasis added). Type 2 diabetics who were overweight tended to be prescribed metformin instead of a sulphonylurea. The indication for Actos suggested it could be used in this group when metformin was not suitable.

Takeda did not consider the comments regarding the NICE guidance to be relevant. Firstly because the promotion of medicine must be in accordance with the terms of its marketing authorization (Clause 3.2) and secondly as the NICE guidance was based on the licensed indications at the time of the review (ie combination use), it was now, effectively, outdated. Indeed if NICE was now to re-review the glitazones it might well place them differently in the hierarchy of pharmacological management of type 2 diabetes.

Takeda did not accept that this question or the overall impression of the advertisement was misleading or in breach of Clauses 3.2 and 7.2.

PANEL RULING

The Panel noted its comments at point 1 above about the place of Actos monotherapy and the overall impression created by the advertisement.

The Panel similarly considered that, in the context in which it appeared, the statement 'Is it time to say Move over Sulphonylurea?', was misleading about the licensed indication of Actos as monotherapy. The description of Actos in the main body of text as an 'excellent alternative to a sulphonylurea' compounded the overall impression given. The Panel ruled a breach of Clause 7.2. The Panel further considered that in the context in which it appeared the statement was inconsistent with the marketing authorization for Actos and thus ruled a breach of Clause 3.2.

3 Term 'Perky Pancreas'

COMPLAINT

Servier considered that the term 'Perky Pancreas', within an advertisement for Actos referred to the state of a pancreas treated with Actos, and alleged that it was thus was an exaggerated claim.

While the term 'perky' was highly subjective, in Servier's view the average reader would consider this to mean 'lively', functioning above expected parameters, or outperforming relative to the norm. The use of the word 'perky; was questionable when referring to the pancreas in patients with type 2 diabetes.

ß-cell function was considered a good indicator of diabetic pancreatic function and was used as such by Takeda in its reply to Servier's initial comments. In type 2 diabetics, reduction in the ß-cell function of the pancreas was generally accepted to occur before abnormalities in blood glucose that led to symptoms and thus diagnosis of the disease. This implied that the pancreas was already somewhat less than 'perky' even before a patient might present for treatment with any symptoms. This was confirmed in the United Kingdom Prospective Diabetes Study (UKPDS), in which newly presenting type 2 diabetics were shown to have decreased pancreatic function by HOMA analysis, the very technique described in the Actos SPC. Furthermore ß-cell function had been shown to continue to decline in patients who were treated initially by diet according to good clinical practice. Servier contended that by the time a patient was taking Actos, there was already likely to be significant pancreatic dysfunction, whether it was being taken second, third or fourth line according to its indication.

Servier noted that Takeda had contended that this was a reference to the claim that pancreatic function was maintained with Actos therapy, as the SPC stated 'HOMA analysis shows that pioglitazone improves beta cell function as well as increasing insulin sensitivity. One year clinical studies have indicated maintenance of this effect'. Servier did not dispute the results of this one year study or that pancreatic function was maintained over one year on Actos. However, this needed to be placed in the context of the condition of the pancreas at the start of therapy, as stated above. Servier noted that in the UKPDS, patients treated for type 2 diabetes with diet, sulphonylurea or metformin all showed an improvement in ß-cell function after one year before a decline in function over the following five. Servier therefore questioned the use of evidence as short term as one year to justify the term 'Perky Pancreas' and its implied superiority to sulphonylureas in the phrase 'Move over Sulphonylurea'.

Finally the study that Takeda used to support its claim (Hanefield and Göke, 2000) focused on the role of pioglitazone in combination with other oral antihyperglycaemic agents in the treatment of type 2 diabetes. The use of this paper to support a claim in a misleading advertisement for the use of Actos in monotherapy was therefore invalid.

Regardless of the validity and robustness of these data, Servier considered that in a type 2 diabetic, the pancreas could not by any definition be described as 'perky' in the sense that this would be viewed by the average reader. Servier alleged that 'Perky Pancreas' was an exaggerated claim in breach of Clause 7.10.

RESPONSE

Takeda submitted that physicians would know that ß-cell function was considered a good indicator of diabetic pancreatic function. Patients at the time of diagnosis and hence also at the time they might be started on Actos monotherapy were likely to have pancreatic dysfunction or ß-cell failure.

Section 5.1 'Pharmacodynamic properties' of the Actos SPC stated: 'HOMA analysis shows that pioglitazone improves beta cell function as well as increasing insulin sensitivity. One year clinical studies have indicated maintenance of this effect'.

Takeda noted Servier's comment that the average reader would interpret 'perky' as 'lively' or 'outperforming relative to the norm'. This advertisement was used in medical press for GPs and hospital doctors and therefore the 'average reader' would fully appreciate that in most type 2 diabetics the 'norm' would be to have a dysfunctional pancreatic state. Hence if Actos could improve the state of the pancreas from its dysfunctional state as shown in these studies it could be thought of as 'perking up' the pancreas.

Takeda submitted that the use of 'perky' did not imply any superiority over sulphonylureas and nor was it intended to.

As the effect of pioglitazone on ß-cell function was part of the SPC Takeda did not need to provide further substantiation by way of a reference. The SPC referred to one year studies and these were studies of pioglitazone in monotherapy. As the study was not yet fully published Takeda did not cite this as a reference.

PANEL RULING

The Panel noted to whom the advertisement was directed and Takeda's submission that the average reader would thus expect a type 2 diabetic to have a dysfunctional pancreas. The phrase 'Perky Pancreas' implied that such a pancreas would improve with treatment. The Panel did not consider that the phrase 'Perky Pancreas' exaggerated the effect of Actos upon the pancreas nor did it imply superiority to sulphonylureas as alleged. No breach of Clause 7.10 was ruled in both regards.

During its consideration of this case, the Panel noted Takeda's submission that as the effect of Actos on beta cell function was included in the SPC then Takeda did not need to provide further substantiation by way of reference. The Code required any information, claim or comparison to be capable of substantiation. It further required such substantiation to be provided without delay at the request of members of the health professions or appropriate administrative staff. It need not be provided, however, in relation to the validity of indications approved in the marketing authorization. The Panel noted that the reference in the Actos SPC to improvements in beta cell function was in Section 5.1, Pharmacodynamic properties, and not in Section 4.1, Therapeutic indications. Such an effect, therefore, appeared to be a benefit of therapy but not the reason to treat. The Panel thus disagreed with Takeda's submission and requested that the company be so advised.

Complaint received **24 October 2003**

Case completed **20 January 2004**

CASE AUTH/1537/11/03 *NO BREACH OF THE CODE*

SEE ME v SANOFI-SYNTHELABO

Promotion of Depakote

The Campaign Director of See Me, a Scottish mental health charity, complained about promotional materials for Depakote (valproate semisodium) which Sanofi-Synthelabo had available on its stand at a national meeting on guidelines for bipolar disorders. See Me considered that an advertisement which featured a parody of the self-portrait of Van Gogh, his ear covered with a modern dressing pad, trivialised the issue and was unlikely to add to the understanding of bipolar disorders.

See Me was more concerned about an advertisement featuring a photograph which appeared to be taken by a person standing on a ledge of a tall building and looking downwards. The wearer's shoes were in the foreground with the road some distance away. The headline read 'I'm on top of the world' below which was stated 'G Evans, aged 32 Acute mania sufferer (untreated)'. Whilst See Me appreciated that suicide could be a consequence of poorly managed mania, it was also aware that treatment for mania, and reduction of risk, did not always include medication. To imply, using that shock image, that Depakote prevented suicide in these circumstances did not reflect the sensitivity with which people with bipolar disorders deserved to be treated and regarded by the medical profession.

The Panel noted that Depakote was indicated for the acute treatment of a manic disorder associated with bipolar disorder. One of the advertisements at issue featured a copy of the self portrait by Van Gogh who had suffered from manic depression. The depiction of the original painting had been altered to show a bandage over the left ear. Given the relevance to the therapeutic area the Panel considered that the majority of health professionals would not share the complainant's view that the advertisement trivialised bipolar disorder and was unlikely to add to the understanding of it. No breach of the Code was ruled.

The Panel noted that the 'shoes' image had been used on a dosage card which gave information about dosage, plasma concentration, speed of response and any precautions needed if Depakote was to be co-prescribed with other medicines. None of the claims referred to the prevention of suicide. The situation shown in the photograph was one in which a patient with bipolar disorder might find themselves and was thus relevant to Depakote's licensed indication. The Panel did not consider that the dosage card suggested that Depakote would prevent suicide in the circumstances depicted and it was thus not misleading as alleged. No breach of the Code was ruled.

The Campaign Director of See Me, the Scottish campaign to eliminate the stigma and discrimination associated with mental health problems, complained about the promotion of Depakote (valproate semisodium) by Sanofi-Synthelabo Limited. The materials at issue were those displayed on Sanofi-Synthelabo's stand at the Scottish Intercollegiate Guideline Networks (SIGN) national meeting on its draft guidelines for bipolar disorders in November in Edinburgh. See Me stated that concerned individuals, both medical professionals and lay, who were offended by the advertisements reported them to the organisation.

COMPLAINT

See Me noted that the first advertisement to cause concern featured a parody of the famous self-portrait by Van Gogh, his ear covered by a modern dressing pad. The caption referred to Depakote's reported ability to rapidly reduce the symptoms of mania. See Me considered that this advertisement trivialised the issue, using a very recognisable image, and was unlikely to add to the understanding of bipolar disorders. See Me noted that some of the other merchandising bearing the image featured the name of the medicine but not the modern dressing.

See Me enclosed a copy of a second advertisement which it considered was substantially more concerning. The advertisement featured a photograph which appeared to be taken by a person standing on a ledge of a tall building and looking downwards. The wearer's shoes were in the foreground with the road below some distance away. The headline read 'I'm on top of the world' below which was stated 'G Evans, aged 32 Acute mania sufferer (untreated)'. Whilst See Me appreciated that suicide could be a consequence of poorly managed mania, it was also aware that treatment for mania, and reduction of risk, did not always include medication. To imply, using that shock image, that Depakote prevented suicide in these circumstances did not reflect the sensitivity with which people with bipolar disorders deserved to be treated and regarded by the medical profession.

See Me stated that it took very seriously all episodes of stigma reported to it, and considered that these advertisements, and particularly the second, sufficiently offensive for it to take action.

See Me worked very closely with people who experienced stigma. One of the most common areas of stigma reported to it was in the delivery of health services, in mental health and in other areas. An area of particular concern was that GPs often had very little knowledge and understanding of mental health problems and how best to treat them. Awareness of bipolar disorder itself, even in the medical profession, was relatively low, and to generalise experiences in this manner was unhelpful.

When writing to Sanofi-Synthelabo, the Authority asked it to respond in relation to Clauses 7.2, 7.8, 9.1 and 9.2 of the Code.

RESPONSE

Sanofi-Synthelabo explained that SIGN had organised the guidelines consultation meeting. A copy of the invitation to the meeting was provided. The majority of the audience were health professionals and the

meeting was advertised as being of interest to 'psychiatrists, community psychiatric nurses, pharmacists, GPs, specialist nurses, public health physicians, clinical psychologists and members of the voluntary sector'.

Lay people representing patient bodies were present in small numbers, and acted in a professional capacity. As such, following an invitation to attend, and in common with a number of other pharmaceutical companies, Sanofi-Synthelabo was present at the meeting with promotional material designed for use with a professional audience.

Sanofi-Synthelabo confirmed that a dosing card (ref DEP-03/024) with the photograph of shoes on top of a building and captioned 'I'm on top of the world' was available at the meeting.

It was not clear to which item See Me referred in connection with the Van Gogh image. This image of the artist, who was thought to have suffered from bipolar disorder, with a modern dressing applied had been used promotionally for the last 3 years. Sanofi-Synthelabo provided a copy of this image, as it appeared on a stand similar to that used at the SIGN meeting. The image of Van Gogh without the modern dressing had only ever appeared on a Depakote wall clock, intended for use in clinical areas; a copy of the artwork was enclosed. An example of the clock was present on the stand although not distributed at this event.

Sanofi-Synthelabo noted that the major concern raised by See Me was that the 'shoes' image might add to the stigma associated with mental health. Sanofi-Synthelabo had a strong CNS heritage and future pipeline of psychiatric products. The company was committed to promoting the well-being of patients with all kinds of mental illness and it had worked extensively with other patient organisations to help foster a better understanding of mental health issues.

Both the 'shoes' and Van Gogh campaigns had been used exclusively in materials for medical professionals and were not intended for use with members of the general public. Clearly the purpose of the advertising was to highlight the importance of bipolar disorder, a condition for which awareness, even amongst the medical community, was relatively low. The majority of patient groups would agree that there was a great need for more attention to be drawn to this much-neglected condition. This need to raise awareness underlined the use of such high impact imagery in Sanofi-Synthelabo's promotional campaigns.

Patients experiencing manic episodes associated with bipolar disorder often displayed high-risk behaviours which could lead to tragic consequences and the use of such imagery to highlight the negative aspects of a condition did not lead to an increase in the stigma associated with that condition. If anything the use of such an image within a professional context would give rise to a greater understanding of the difficulties faced by some patients suffering from bipolar disorder.

In its complaint See Me suggested that the Van Gogh image might trivialise mental health issues. The use of such a familiar image of a famous and much loved painter could be argued to reduce stigma. If Van Gogh was indeed a sufferer of bipolar disorder, it was clear that it was possible for patients with this disorder to function at a high level.

It seemed from looking at these two images together that Sanofi-Synthelabo was taking a responsible position in attempting to promote, within a professional context, a better understanding of bipolar disorder as a serious condition. The company did not consider therefore that its advertising promoted stigma or trivialised this serious mental disorder.

During the development of both sets of images Sanofi-Synthelabo's internal procedures concerning approval of promotional items were followed. Both the 'shoes' and Van Gogh images were shown to several focus groups of psychiatrists prior to their adoption. At no stage in this process were any concerns raised amongst these groups as to the suitability of either image.

Sanofi-Synthelabo considered that it was unlikely that clinicians would raise any concerns about the Van Gogh images. Indeed it did not appear that See Me was arguing that this image was likely to cause offence, rather that it 'trivialised' the condition and was 'unlikely to add to the understanding of bipolar disorders'.

The Van Gogh image had been used over the last 3 years, and this was the first complaint about the campaign that Sanofi-Synthelabo had received. Given its high visibility, it seemed therefore that by definition it was unlikely to have caused offence to the majority of its intended viewers. The Van Gogh journal advertisement had been the subject of positive correspondence in the BMJ; a copy was provided. In this independent BMJ discussion the author praised the appropriateness of the image and the important messages that it conveyed.

Sanofi-Synthelabo noted that the 'shoes' image was always intended to be used only in advertising for doctors. The image graphically displayed the danger that existed from being figuratively 'on top of the world'. The company accepted that the image was impactful, but considered that it should be seen in the context of the entire piece. In Sanofi-Synthelabo's view the image was not likely to cause offence to psychiatrists, as they were very familiar with such high-risk behaviours commonly exhibited by their patients. The image was designed to link such high-risk behaviour, which was commonly associated with other mental illnesses, with a manic episode. It was possible to view the euphoria associated with mania in a positive light and not fully appreciate the dangers associated with such a state of mind.

Sanofi-Synthelabo noted that following receipt of this complaint it had informally consulted a leading mental health charity and its views were that the 'shoes' image was suitable for use with psychiatrists and would be helpful in highlighting the need to effectively manage bipolar illness. Thus the company defended the use of this imagery as being neither offensive to psychiatrists, nor misleading either directly, or in any way by implication. The company's extensive use of this image in one-to-one calls and in mailings to psychiatrists had not indicated that it was likely to cause offence.

Sanofi-Synthelabo noted that the Authority had asked it to provide data on Depakote's effect on the treatment of suicide. As there was no direct claim for suicide prevention in the advertisement, the company could only assume that the Authority would consider whether the image could be construed to make an indirect claim of suicide prevention.

The 'shoes' image was intended to highlight the importance of treating mania actively. The image need not imply that the individual was about to attempt suicide. The headline 'On top of the world' was intended to distinguish the patient with mania from the one who was about to commit suicide. The description 'On top of the world' would be an unlikely description of someone who was intending to kill themselves. Given the specialist audience for this material, there was little doubt that such an interpretation would be held by most psychiatrists. Suicide in classic acute mania was rare.

The image deliberately contrasted the patient's euphoria with the clear and present risk he was in due to his position on top of the world. He might well be euphoric and in his exhilarated state was looking down on the world below oblivious to the risk he had placed himself in.

The core symptoms of mania included impulsive, dangerous, risk taking behaviour. Since this type of behaviour was a core part of mania, particularly in mixed episodes, even were an inference of suicide efficacy to be made from the image, this should be seen in the context of the treatment of a high-risk manic episode for which Depakote was a licensed treatment.

Prevention of suicide was not intended as a claim in the piece (nor indeed did Sanofi-Synthelabo consider that the image implied this). The name of the medicine was not present on the same page as the image, thus taking a further step back from any suggestion of an anti-suicide claim.

Sanofi-Synthelabo recognised that it would be irresponsible to use this image were there no suggestion that Depakote might help to reduce the risk in the short-term of dangerous, high-risk behaviour. The company summarised the clinical evidence to support the notion that treatment with Depakote of an individual who was manic and exhibiting impulsive behaviour could reasonably be expected to reduce his risk in the short term.

As already outlined, Sanofi-Synthelabo considered that the 'shoes' image should be interpreted as representing an acute manic episode. Depakote was licensed for the treatment of mania. Results could be expected within 1-4 days of treatment initiation, and as such treatment of a high-risk individual with mania could make a significant and early impact on their illness (Pope *et al*, 1991). Hirschfield *et al*, (2003) had demonstrated that early treatment with high dose Depakote was important to the speed of response.

The advertisement needed to be seen in the context of raising awareness of a real and significant problem that was sadly often neglected. Depakote was one of the available treatments for mania, and given the risks that mania presented, the advertisement sought to advocate its early, more widespread use at appropriate doses.

Sanofi-Synthelabo submitted that each claim in question was supported by the literature. There were no comparisons made with other products. The claims made were accurate, balanced, fair and objective.

The dosing card contained simple tables that presented the data clearly. The 'shoes' image conformed to the Code since it did not make any direct or indirect claim. Even if taken to have an indirect claim, Sanofi-Synthelabo considered that there was sufficient data to suggest that an untreated individual with mania would be likely to respond to Depakote even in the presence of depressive symptoms associated with mania. As such the company considered that the artwork complied with the letter and spirit of the Code.

Sanofi-Synthelabo stated that in summary the materials were encountered by representatives of See Me whilst attending a SIGN guidelines consultation meeting. The meeting was open to medical professionals and lay persons acting in a professional capacity as representatives of patient groups. Sanofi-Synthelabo attended the meeting at the invitation of SIGN and in association with a number of other pharmaceutical companies.

The 'shoes' and Van Gogh campaigns were intended to raise awareness of the serious nature and consequences of bipolar disorder. They were intended to encourage medical professionals to engage in the management of patients and as such neither trivialised this important condition nor encouraged stigma. Other patient groups asked to comment on these materials had indicated their support for this initiative.

The 'shoes' campaign was intended to raise awareness of the high-risk behaviours often demonstrated by patients experiencing a manic episode. No claim of a reduction in suicidal behaviour was intended or inferred. Depakote was however a proven treatment for the management of acute manic episodes and as such had been demonstrated to reduce the risk of such high-risk behaviours.

PANEL RULING

The Panel noted that Clause 9.1 of the Code required high standards to be maintained at all times. Clause 9.2 required that all materials must recognise the special nature of medicines and the professional nature of the audience to which they were directed and must not be likely to cause offence.

The Panel noted that Depakote was indicated for the acute treatment of a manic disorder associated with bipolar disorder. One of the advertisements at issue featured a copy of the self portrait by Van Gogh who had suffered from manic depression and who had cut off part of his left ear. The depiction of the original painting had been changed to show a bandage, held in place by two strips of adhesive dressing, over the left ear.

The Panel noted that the complainant considered that the advertisement trivialised the condition and was

unlikely to add to the understanding of bipolar disorder. Given the therapeutic area and the relevance of the painting depicted in the advertisement the Panel considered that this view would not be shared by the majority of health professionals. The image of Van Gogh was easily recognisable, it was well known that he had suffered from manic depression and that he had cut off part of his left ear. The Panel considered that the advertisement was not unreasonable in relation to the requirements of Clauses 9.1 and 9.2 and no breach of those clauses was ruled.

With regard to the 'shoes' advertisement the complainant had found the image shocking and considered that to imply that Depakote prevented suicide in those circumstances did not reflect the sensitivity with which people with bipolar disorders deserved to be treated, and regarded by the medical profession. The Panel noted that at the SIGN meeting the 'shoes' image had been used on page one of a four page dosage card. Page two was headed 'Optimising dosing for fast results' and gave, *inter alia*, details of the doses of Depakote required according to bodyweight given that effective doses were usually around 20mg/kg/day or 1-2g/day. Target plasma concentrations and speed of response were also referred to on page two. Page three gave details of precautions needed, if any, if Depakote was to be used in combination with other antipsychotics or antidepressants. The prescribing information appeared on page four. None of the claims in the dosage card referred to prevention of suicide. The Panel again noted the therapeutic area and Sanofi-Synthelabo's submission that patients experiencing manic episodes associated with bipolar disorder often displayed high-risk behaviours which could lead to tragic consequences. The situation depicted was thus one in which patients with bipolar disorder might find themselves and was thus relevant to Depakote's licensed indication. In the Panel's view the majority of health professionals would not find the image shocking. The Panel did not consider that the dosage card suggested that Depakote would prevent suicide in the circumstances depicted on the front page. It was thus not misleading as alleged and the Panel ruled no breach of Clauses 7.2 and 7.8. The Panel further considered that in the context in which it was used the 'shoes' image was not unreasonable in relation to the requirements of Clauses 9.1 and 9.2 of the Code. No breach of those clauses was ruled.

The Panel noted that, in addition to health professionals, the SIGN meeting was advertised as being of interest to, *inter alia*, members of the voluntary sector. The audience was thus likely to consist of those who were health professionals and those who were not. The complainant referred to 'lay' people who saw the advertisements. Sanofi-Synthelabo had made material available from its stand which had been for use with health professionals and which was not intended for use with members of the general public. The Panel noted the company's submission that the lay people who were present at the meeting, representing patient bodies, were acting in a professional capacity and so could be shown material aimed at health professionals. The Code did not make provision for 'professional lay people'. The Code applied to the promotion of medicines to health professionals and to appropriate administrative staff. In the Panel's view lay people who worked, either voluntarily or otherwise, for a patient group and who were not also a health professional, could not be regarded as appropriate administrative staff. 'Appropriate administrative staff' was interpreted as referring to practice managers and NHS finance directors, ie people employed within hospitals, health authorities, primary care groups and the like. The Panel considered that 'members of the voluntary sector', as referred to in the invitation to the SIGN meeting, could include local fundraisers. The Panel did not know the professional qualifications of those who had attended on behalf of patient groups. Nonetheless the Panel was concerned that Depakote had been promoted to members of the public albeit that they were associated with interested patient groups. In circumstances where a mixed audience was in attendance then all material on pharmaceutical company stands had to be suitable for the general public. The Panel requested that Sanofi-Synthelabo be reminded of the provisions of Clause 20.1 which prohibited the promotion of prescription only medicines and certain other medicines to the general public.

Complaint received **24 November 2003**

Case completed **19 January 2004**

CASE AUTH/1538/12/03

UNIVERSITY DOCTOR v NOVARTIS

Promotion of Sandostatin LAR

A university doctor complained that in a mailer and two leavepieces, Novartis was claiming that its product Sandostatin LAR (octreotide long acting intramuscular injection) controlled the symptoms associated with carcinoid syndrome better than lanreotide (Somatuline Autogel) marketed by Ipsen. The complainant alleged that the data to support this was misleading since it was derived from two separate studies and was thus not a direct comparison of the two products. The studies had different patient populations and designs. One of the studies had only been presented as an abstract at an international meeting; it had not been subject to rigorous scientific review or published in a reputable scientific journal.

The Panel noted that in the first leavepiece the Sandostatin LAR efficacy data ie percentage improvement in flushing (75-91%) and diarrhoea (46-62%) appeared in one table with the corresponding table of data for lanreotide (43% and 22% respectively) immediately below. Both the heading 'Responder rates at 6 months for Sandostatin LAR and lanreotide Autogel deep sc' and the claim 'Sandostatin LAR – improved control of episodes of diarrhoea and flushing compared with lanreotide Autogel in NETs [neuroendocrine tumors]' were followed by two references, Rubin *et al* (the Sandostatin LAR study) and Ruszniewski (the lanreotide study). The leavepiece also included adverse event data from the studies. The Sandostatin LAR adverse event data was shown in a bar chart with the lanreotide Autogel data similarly displayed immediately below. The headings to the lanreotide Autogel efficacy data and to both presentations of the adverse event data referred to a footnote beneath the adverse event data which stated 'These data do not represent a direct comparison to Sandostatin LAR'.

In the Panel's view the presentation of the data was such that most readers would assume that there was data directly comparing the efficacy of Sandostatin LAR with lanreotide and that Sandostatin LAR was the superior medicine. Although the efficacy data for each product was shown in separate tables there was no clear indication that the data were from two separate studies; the footnote was inadequate in this regard. The same colouring was used for both tables and they appeared together in one boxed area of the leavepiece. The impression that the data came from one study was further strengthened by the claim 'Sandostatin LAR – improved control of episodes of diarrhoea and flushing compared with laneotide Autogel in NETs' which appeared above the tables of data. Thus the Panel considered that the comparison as presented was misleading and could not be substantiated. Breaches of the Code were ruled. Given its ruling the Panel did not consider it was necessary to go on to decide whether it was valid to compare the data from the two studies.

The Panel noted that in the second leavepiece headed 'Sandostatin LAR and lanreotide Autogel deep sc in the treatment of the symptoms of neuroendocrine tumours', the subheading 'Cost and Response rate comparisons' was followed by a comparison chart which included the efficacy data for Sandostatin LAR and lanreotide referenced to Rubin *et al* and Ruszniewski respectively. Although a footnote immediately beneath the comparison chart explained that the data had not come from a direct head to head study between Sandostatin LAR and lanreotide Autogel deep sc the Panel did not consider that this negated the impression that it had. The Panel considered that its ruling above applied here and breaches of the Code were ruled.

The Panel noted that the mailing, headed 'Which would your patients prefer?', included the claim 'Sandostatin LAR has demonstrated improved control of episodes of diarrhoea and flushing compared with lanreotide Autogel in NETs'. As with the leavepieces considered above, the mailing compared the data from Rubin *et al* and Ruszniewski; the Panel did not consider that the impression that the results were from a direct comparison was negated by a footnote explaining that they were not. The Panel considered that its rulings with regard to the first leavepiece also applied here and further breaches of the Code were ruled.

A university doctor complained about the promotion of Sandostatin LAR (octreotide long acting intramuscular injection) for the treatment of neuroendocrine tumours (NETs) by Novartis Pharmaceuticals UK Ltd. The materials at issue were a mailer sent in September 2003 (SAN 03000950), a leavepiece used since September 2003 (SAN 03001324) and a leavepiece used since July 2003 (SAN 03001062).

COMPLAINT

The complainant stated that there was little doubt that Sandostatin LAR treatment improved symptoms, such as flushing and diarrhoea, in neuroendocrine tumours. The material however, claimed superior control of symptoms associated with carcinoid syndrome compared with lanreotide (Somatuline Autogel) marketed by Ipsen Limited. The complainant alleged that the data to support this assertion was misleading since it was derived from two separate studies and did not represent a direct comparison of the two products. The studies represented different patient populations and different study designs. One of the studies was an abstract presented at an international meeting. This had not been subject to rigorous scientific review or published in a reputable scientific journal.

The complainant believed that the available scientific evidence showed that both products were effective at improving diarrhoea and flushing in patients with carcinoid syndrome. There had been no direct comparative studies between the products.

When writing to Novartis the Authority drew attention to Clauses 7.2, 7.3, 7.4 and 7.8 of the Code.

RESPONSE

Novartis stated that Sandostatin LAR was indicated for the relief of symptoms associated with gastroenteropancreatic tumours including carcinoid tumours with features of carcinoid syndrome, VIPomas and glucagonomas, in patients whose symptoms were adequately controlled on subcutaneous treatment with Sandostatin. Sandostatin was not antitumour therapy and was not curative in these patients.

Somatuline Autogel was indicated for the treatment of symptoms associated with neuroendocrine (particularly carcinoid) tumours.

Leavepiece SAN 03001324 was entitled 'Confident control in the treatment of neuroendocrine tumours (NETs)'. Novartis stated that neuroendocrine tumours were a diverse group including carcinoid tumours, insulinomas, glucagonomas, VIPomas, gastrinomas, somatostatinomas, PP-omas (pancreatic polypeptide) etc.

Inside the leavepiece a banner heading ran across both pages 'Responder rates at 6 months for Sandostatin LAR and lanreotride Autogel deep sc' referenced to two studies; Rubin *et al* (1999) which studied Sandostatin LAR and Ruszniewski (2002) which studied lanreotide. The Ruszniewski data was presented at an Ipsen-sponsored satellite symposium of the European Federation of Endocrine Societies meeting in April 2003 and although it had not yet been published in a 'reputable scientific journal', as noted by the complaint, this same data had been used by Ipsen in its promotion of lanreotride and referenced to a presentation given by Ruszniewski at the UKNETwork meeting in May 2003 as well as to data on file. Novartis therefore assumed that Ipsen considered that this data represented the most up-to-date (and presumably positive) available on lanreotide.

Novartis stated there were no direct comparisons of Sandostatin LAR and lanreotide Autogel in neuroendocrine tumours. However, in Novartis' view this did not make an indirect comparison invalid. In clinical practice it was entirely valid to compare products with similar modes of action in order to make treatment decisions on both a cohort and individual patient level, and it was not unreasonable for a company to present this data provided that it was done responsibly.

The two studies included patients of comparable severity and were of broadly similar design, although clearly the amount of information given in the abstract was significantly less than that in the full paper. Both studies involved patients with carcinoid tumours with the aim of assessing symptoms, specifically flushing and diarrhoea as well as recording side effect data.

In the Sandostatin LAR study, patients were eligible if they initially had symptoms controlled on subcutaneous octreotide ie ≤2 flushing episodes per day and an average stool frequency of ≤3 per day, which then returned during a wash-out (medicine free) period to 3 episodes of flushing in a single day and/or an increase of at least 2 stools a day above the pre wash-out period. Ninety three patients were recruited in the intention-to-treat (ITT) population and randomised to one of four groups: subcutaneous octreotide, or Sandostatin LAR (10, 20 or 30mg). The Sandostatin LAR groups were double-blinded and remained so until the end of the study period at six months ie no up or down titration was allowed although subcutaneous octreotide was allowed for breakthrough symptoms, as in the lanreotide study. Of the 93 ITT patients, 67 were randomised to Sandostatin LAR (one of the 3 doses), and it was this group that was used in the leavepiece.

In the lanreotide study, patients were initially untreated (and therefore analogous to the Sandostatin LAR patients in the wash-out period) and were eligible if they had ≥3 stools per day and/or ≥1 moderate or severe flushes per day. Seventy one patients were recruited all of whom received 90mg Autogel intramuscularly for the first 2 months with the dose being titrated up or down (to 120 or 60mg respectively) for the remaining 4 months according to response, with subcutaneous octreotide allowed for breakthrough symptoms. The study was open-label.

Novartis submitted that the studies involved similar numbers of patients on intramuscular therapy and either a randomisation or a titration to three different dose levels.

The results of both studies were presented in the leavepiece under the two page banner headline. It was quite clear from the outset that the studies were separate – two references were given, there were two charts/graphs (one for each study) one beneath the other, not side by side, for efficacy and side effects and a statement was made at the bottom of the right hand page that 'These data do not represent a direct comparison to Sandostatin LAR'. Each chart/graph was clearly labelled in large type to indicate to which product it referred.

In terms of the efficacy data presented the reductions in symptoms of flushing and diarrhoea were given as these were primary end points in both studies. For Sandostatin LAR a range of improvement was given reflecting the randomisation to the three dose levels. For lanreotide a single figure for improvement was given in the abstract despite the range of potential doses. For side effects, the abstract on lanreotide stated 'The incidence of the most common drug-related adverse events were abdominal pain (20%), fatigue (13%) and cholelithiasis (10%)'. For Sandostatin LAR, the most common treatment-related adverse event (given in table 3 of the paper) was cholelithiasis which occurred in 3 of 67 patients (4.5%). The figures for diarrhoea (steatorrhoea) and abdominal pain were shown as these were also given for lanreotide.

Novartis submitted that the data presented were accurate, balanced (the study populations and designs were broadly similar), fair, objective and unambiguous (it was explicit that the two studies were separate). When this leavepiece was printed in early September 2003 it was also the most up-to-date data available. Since then, however, a further presentation (not a full paper) of the lanreotide data had been given at the European Cancer Conference meeting. This new presentation still included the 71

patients, and the percentage improvement for flushing and diarrhoea was identical to the Ruszniewski abstract eg reduction from baseline for flushing of –56%, equating to an improvement of 43%. However, the side effect profiles attributable to treatment were now reported as abdominal pain 38%, diarrhoea 17% and cholelithiasis 10%. Novartis had not updated the leavepiece to reflect these new figures. However, it considered that the leavepiece was not in breach of Clause 7.2 for the above reasons.

For similar reasons the leavepiece did not mislead. Under Clause 7.3 comparisons were permitted if they did not mislead, and it was clear here that two separate studies were discussed. The two medicines were intended for the same purpose and several material, representative, relevant and substantiable features were compared. The leavepiece was not therefore in breach of Clause 7.3.

Novartis submitted that all the data presented were capable of substantiation by the references cited.

The leavepiece was not therefore in breach of Clause 7.4. The graphs and charts were clearly labelled, and presented, as demonstrated above, in a balanced and factual way, and were entirely relevant to the claims made in the piece. The leavepiece was not therefore in breach of Clause 7.8.

Novartis confirmed that the above response applied to the mailer, SAN 03000950 and the leavepiece, SAN 03001062.

PANEL RULING

The Panel considered each item separately.

Leavepiece SAN 03001324

The Sandostatin LAR efficacy data ie percentage improvement in flushing and diarrhoea (75-91% and 46-62% respectively) appeared in one table with the corresponding table of data for lanreotide (43% and 22% respectively) immediately below. Both the heading 'Responder rates at 6 months for Sandostatin LAR and lanreotide Autogel deep sc' and the claim 'Sandostatin LAR – improved control of episodes of diarrhoea and flushing compared with lanreotide Autogel in NETs' were followed by two references, Rubin *et al* and Ruszniewski. The leavepiece also included adverse event data from the studies. The Sandostatin LAR adverse event data was shown in a bar chart with the lanreotide Autogel data similarly displayed immediately below. The headings to the lanreotide Autogel efficacy data and to both presentations of the adverse event data were followed by a obelus, the explanation for which was given by a footnote beneath the adverse event data which stated 'These data do not represent a direct comparison to Sandostatin LAR'.

In the Panel's view the presentation of the data was such that most readers would assume that there was data directly comparing the efficacy of Sandostatin LAR with lanreotide and that Sandostatin LAR was the superior medicine. Although the efficacy data for each product was shown in separate tables there was no clear indication that the data were from two separate studies; the footnote was inadequate in this regard. The same colouring was used for both tables and they appeared together in one boxed area of the leavepiece. The impression that the data came from one study was further strengthened by the claim 'Sandostatin LAR – improved control of episodes of diarrhoea and flushing compared with laneotide Autogel in NETs' which appeared above the tables of data. Thus the Panel considered that the comparison as presented was misleading and could not be substantiated. Breaches of Clauses 7.2, 7.3, 7.4 and 7.8 of the Code were ruled. Given its ruling the Panel did not consider it was necessary to go on to decide whether it was valid to compare the data from the two studies.

Leavepiece SAN 03001062

The leavepiece was headed 'Sandostatin LAR and lanreotide Autogel deep sc in the treatment of the symptoms of neuroendocrine tumours'. The subheading 'Cost and Response rate comparisons' was followed by a comparison chart which included percentage improvements in flushing episodes and diarrhoea episodes for the products. In both respects the data for Sandostatin LAR was more favourable than that for lanreotide. The Sandostatin LAR flushing and diarrhoea data was referenced to Rubin *et al*. The lanreotide Autogel data was referenced to Ruszniewski.

Although it was stated immediately beneath the comparison chart that 'This presentation does not compare data from a direct head to head study between Sandostatin LAR and lanreotide Autogel deep sc' the Panel did not consider that this negated the impression that the data had come from a direct comparison study which showed a benefit for Sandostatin LAR.

The Panel considered that its ruling at point 1 also applied here. Breaches of Clauses 7.2, 7.3, 7.4 and 7.8 of the Code were ruled.

Mailer SAN 03000950

The mailing was headed 'Which would your patients prefer?' and the front page included the claim 'Sandostatin LAR has demonstrated improved control of episodes of diarrhoea and flushing compared with lanreotide Autogel in NETs' which was referenced to Rubin *et al* and Ruszniewski. Page 3 of the mailer provided the data in two separate tables beneath the heading 'Responder rates for Sandostatin LAR and lanreotide Autogel deep sc'. An obelus was used next to the heading to the lanreotide Autogel table with the explanation 'These data do not represent a direct comparison to Sandostatin LAR'. The Panel did not consider, however, that this negated the impression that the data came from a direct comparison study.

The Panel considered that its ruling at point 1 above also applied here. Breaches of Clauses 7.2, 7.3, 7.4 and 7.8 of the Code were ruled.

Complaint received **1 December 2003**

Case completed **10 February 2004**

CASE AUTH/1539/12/03

VOLUNTARY ADMISSION BY LILLY

Conduct of representative

Lilly voluntarily advised the Authority that one of its contract representatives had made claims for Cialis (tadalafil) which were subsequently broadcast on a local radio show.

Lilly explained that on the way to work the representative heard a quiz on a local radio show which involved identifying the year suggested by the clues; 'Which year did David Beckham wear a sarong?' and 'Which year was Viagra launched?'. The representative telephoned the radio station and spoke to a presenter off-air. She knew she was off-air as she could still hear music on her car radio. The representative told the presenter that she knew that the year was 1998 because she worked for 'a company that made a competitor to Viagra'. The representative continued by telling the presenter that the competitor product '[is] called Cialis and works for 24 hours, whereas Viagra works for about 4 hours'. The two of them continued to have a conversation about erectile dysfunction and then the presenter finished by thanking the representative for plugging the product. The representative knew that she was still off-air as the radio was still playing music and she expected to be told to stay on the line until the song had finished and she would then answer the question again, this time live, on air. Instead, the presenter said he would be sending her a prize and thirty seconds later she heard her discussion with him broadcast on the air, in full. The representative immediately realised her error and reported the incident to her line manager.

The Director of the Authority decided that as the matter related to the promotion of a prescription only medicine to the general public it was sufficiently serious for it to be taken up and dealt with as a complaint under the Code. This was consistent with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review.

The Panel noted that the representative had made claims regarding the benefits of Cialis which had been broadcast on local radio. Although the representative had made the remarks off-air, and had not realised that they would be broadcast, she had knowingly made them to a radio presenter during the course of his radio programme. The representative had volunteered the information about Cialis. The Panel noted that the representative had realised her mistake as soon as her discussion with the presenter was broadcast and that she had immediately reported the matter to her line manager. The Panel considered that such action was commendable. Nonetheless, the Panel also considered that in making claims for Cialis as she had done the representative had not maintained a high standard of ethical conduct. A breach of the Code was ruled. The representative had also, in effect, promoted Cialis, a prescription only medicine, to the general public. A further breach of the Code was ruled.

COMPLAINT

Eli Lilly & Company Limited voluntarily advised the Authority that one of its contract representatives had made claims for Cialis (tadalafil) which were subsequently broadcast on a local radio show.

Lilly explained that on the way to work the representative heard a quiz on the local radio show, '2-Ten FM', which covered Berkshire and North Hampshire. The quiz, 'Guess the year?', involved identifying the year suggested by two clues. The clues in question were 'Which year did David Beckham wear a sarong?' and 'Which year was Viagra launched?'.

The representative stopped her car and made several attempts to telephone the radio station on her mobile. When she got through she spoke to a presenter off-air. She knew she was off-air as her car radio was still audibly playing music from the radio station in the background. Indeed throughout the conversation she knew she was off-air and assumed the presenter was having a warm-up discussion, as this had been her previous experience with another radio station, 'Capital FM'.

The presenter asked her for her answer and she stated, '1998 was the year in which Viagra was launched'. The presenter confirmed she was correct. The representative then told the radio presenter that she knew the answer because she worked for 'a company that made a competitor to Viagra'. She then asked him if he knew what that was. He replied that he didn't know and asked her 'What is it?'. She replied 'It's called Cialis and works for 24 hours, whereas Viagra works for about 4 hours'. The presenter joked, 'That gave men a lot more fun' and she replied, 'It certainly gave them more time to have fun'. The presenter continued by asking if her husband took Viagra. She laughed and said he didn't need it but 'it's a Godsend for men with erectile dysfunction'. The presenter then finished by thanking her for plugging the product.

The representative knew that she was still off-air as the radio was still playing music and she expected to be told to stay on the line until the song in the background finished and he would then ask her the question again, this time live, on air. Instead, the presenter said he would be sending her two tickets to the cinema in Reading or Basingstoke and took her home address. Thirty seconds later she heard her discussion with the presenter broadcast on the air, in full.

The representative immediately realised her error and reported the incident to her line manager as soon as she arrived at work. Lilly contacted her employer and requested that disciplinary action be taken in relation to this incident in accordance with their internal disciplinary procedures. Lilly also contacted the Authority about the matter.

The representative's employer held a disciplinary hearing and a final written warning was issued. In

arriving at this sanction it was acknowledged that she had not intended to promote Cialis to the general public and that she had acted honestly and professionally in reporting the matter as soon as it had occurred.

Lilly stated that all aspects of the Code were reinforced upon the individual by line management, however the fact that the individual immediately recognised her error indicated that a good level of knowledge and understanding of the Code already existed.

The Director of the Authority decided that as the matter related to the promotion of a prescription only medicine to the general public it was sufficiently serious for it to be taken up and dealt with as a complaint under the Code. This was consistent with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review.

The Authority requested that Lilly respond in relation to the provisions of Clauses 15.2 and 20.1 of the Code.

RESPONSE

With regard to Clause 15.2 of the Code Lilly stated that this was a case of a representative making an isolated error in unusual circumstances. Statements were made in the heat of the moment and immediately realised to be entirely inappropriate. Whilst Lilly accepted that the circumstances were ones to which the Code applied, it considered that it was understandable that the Code might not have been foremost in the representative's mind when she impromptu entered a radio competition on her way to work. Clearly the representative had not intended to promote the product to the general public. The representative acknowledged that she had learnt a valuable lesson about being professional at all times and taking more time to think before acting.

The representative was clearly aware of her obligations under the Code as she immediately realised her error. By immediately contacting her line manager and advising him of the error she accounted for herself well in the circumstances. Clearly others could have taken a different approach. Bearing in mind all of the facts in this case, Lilly considered that the representative had not breached Clause 15.2 in that her handling of this unfortunate situation and her understanding of the Code had demonstrated high standards of ethical conduct and an intention to comply with all relevant requirements of the Code. She had also been punished for her error.

With regard to Clause 20.1 of the Code, Lilly stated that the representative was under the impression she was off-air whilst making the comments to the presenter and therefore only made the statements to one individual. She was not aware that the statements would be broadcast and her consent to that happening was not obtained. Lilly thus considered that this was not a breach of Clause 20.1 on the basis that one individual did not constitute the general public. If a conversation between two individuals along these lines was to constitute the advertising of a prescription only medicine to the general public one was left with the impression that there could be many breaches of Clause 20.1 that took place on a regular basis.

Lilly understood that the information contained in its voluntary admission constituted the entire exchange between the presenter and the representative and that this was what was broadcast. The company did not have a copy of the transcript of the broadcast although it did contact the presenter for his version of events. A copy of the minutes of this call were provided.

PANEL RULING

The Panel noted that the representative in question was a contract representative. The supplementary information to Clause 15 stated that companies employing or using contract representatives were responsible for their conduct and must ensure that they complied with the provisions of Clause 15 and all other relevant clauses of the Code. Lilly was thus responsible for the representative's actions.

The representative had made claims regarding the benefits of Cialis which had been broadcast on local radio. Although the representative had made the remarks off-air, and had not realised that they would be broadcast, she had knowingly made them to a radio presenter during the course of his radio programme. The representative had volunteered the information about Cialis. The Panel noted that the representative had realised her mistake as soon as her discussion with the presenter was broadcast and that she had immediately reported the matter to her line manager. The Panel considered that such action was commendable. Nonetheless, the Panel also considered that in making claims for Cialis as she had done the representative had not maintained a high standard of ethical conduct. A breach of Clause 15.2 was ruled. The representative had also, in effect, promoted Cialis, a prescription only medicine, to the general public. A breach of Clause 20.1 was ruled.

Proceedings commenced 10 December 2003

Case completed 22 January 2004

CASE AUTH/1540/12/03

HOSPITAL PHARMACIST v AVENTIS PHARMA

Conduct of representatives

A senior hospital pharmacist complained about the conduct of representatives from Aventis Pharma. At a cardiology academic meeting attended by the complainant, all the consultants and junior medical staff, a hospital cardiovascular specialist representative from Aventis, accompanied by his supervisor, gave a short presentation. He announced that he was trying very hard to get the hospital to change over from Pfizer's low molecular weight heparin, Fragmin, to Aventis' product Clexane. In the informal conversations that followed the complainant twice heard the Aventis representative state that he would not be surprised if Fragmin was eventually withdrawn given the take-over of Pharmacia by Pfizer. This put doubt in the mind of at least one of the consultants. The representative also stated that the local Pfizer representative had been 'sacked', and there was no replacement actively promoting Fragmin. The complainant noted that the first statement was not true. Before the two representatives left the complainant told them of her discontent at their criticism of another company. From what the medical admissions consultant had told her the previous day, they had been saying the same thing to other doctors in the hospital.

The Panel noted Aventis' submission that one of its representatives had stated that Pfizer's level of representative support for Fragmin had been reduced and that its local representative no longer worked for the company. While it was not possible to determine exactly what had been said it was clear that the current decreased level of representative support for Fragmin by Pfizer had been discussed. The Panel did not know whether the representatives had initiated this topic of conversation, nonetheless they could be seen as casting doubt upon Pfizer's ability to support the product and its commercial viability.

The Panel noted that the complainant stated that doubts had been put in the mind of at least one consultant and that the representatives had been saying the same thing to other doctors in the hospital. The Panel considered that, on balance, by discussing Pfizer's currently reduced local support for Fragmin, the Aventis representatives had failed to maintain a high standard of ethical conduct and had failed to comply with all relevant requirements of the Code. Breaches of the Code were ruled.

The Panel noted that a ruling of a breach of Clause 2 was seen as a sign of particular censure and it did not consider that the issue warranted such censure.

A senior hospital pharmacist complained about the conduct of representatives from Aventis Pharma Ltd.

COMPLAINT

The complainant explained that she participated in the cardiology academic programme meetings each Friday morning, which were attended by all the consultants and junior medical staff. A pharmaceutical company representative, who was allowed a few minutes to promote his/her products, often provided sandwiches. On 28 November 2003 it was the turn of a hospital cardiovascular specialist representative for Aventis, who was accompanied by his supervisor. At the beginning of his presentation he announced that he was trying very hard to get the hospital to change over from Pfizer's low molecular weight heparin, Fragmin, to Aventis' product Clexane. What he said in his talk was alright – comparing trials for the two heparins. However, afterwards whilst talking informally to groups of doctors, he twice said words to the effect that, now that Pfizer had taken over Pharmacia, it could withdraw Fragmin from the market. This put doubt in the mind of at least one of the consultants. He also said that the Pharmacia representative had been sacked in the take-over, which he was not! He then stated that Pfizer no longer had any local medical representative cover for Fragmin.

The complainant stated that at the end of the session she spoke to the two representatives and expressed her opinion that they should not make statements about rival companies which were not founded on fact. Her words did not seem to make much impression. From what the medical admissions consultant had told her the previous day, they had been saying the same thing to other doctors in the hospital.

The Authority asked Aventis to respond in relation to Clauses 2, 9.1 and 15.2 of the Code.

RESPONSE

Aventis acknowledged that the perception and subsequent recall of events and what was said during conversations was more important in the practice of good communication than the actual words and phrases used at the time. The company stated that its representatives had different recall of the answers that they gave to questions they were asked and the conversations that took place on the day to that recalled by the complainant.

Aventis explained that after the presentation the representatives discussed the service levels that the company could provide to the local NHS trust if it changed from Fragmin to Clexane. During this discussion one representative explained that the level of representative support for Fragmin had been reduced following the recent Pharmacia/Pfizer merger and that the local representative was no longer employed by the company. The representative believed this to be correct. Neither representative could remember stating that Pfizer would withdraw Fragmin from the UK market as recalled by the complainant. Both believed that such an action would be extremely unlikely and they could not think how this conclusion could have been reached.

Aventis had contacted Pfizer and established that the local Pfizer representative had retired from the company and was not sacked.

Aventis stated that in conclusion, it appeared that there was a difference of recall of the conversations that took place on 28 November. This was always to be regretted and each business unit director had been instructed to re-emphasise the need for high standards at all times from sales representatives. In particular, they had been asked to stress the need for representatives to appreciate what messages their customers might be taking away and whether it was the same message as the one that they thought they delivered.

Finally, Aventis noted that when the complainant spoke to the representatives in question about her concerns after the presentation they apologised to her for any misunderstanding that there might have been.

In response to a request for further information Aventis stated that, following discussions with Pfizer, it understood that the company had no representative working the territory at the time of the meeting.

Aventis' response was sent to the complainant for comment.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant explained that the representative gave a few minutes' presentation at the end of the cardiology academic programme, after which the doctors started to eat the sandwiches which had been provided. In the informal conversations that then took place the complainant twice heard the representative state that he would not be surprised if the company eventually withdrew Fragmin with the take-over of Pharmacia by Pfizer. He also stated that the local Pfizer representative had been 'sacked', and there was no replacement actively promoting Fragmin. The complainant noted that the first statement was not true, however the second was, but in many ways it was an advantage not having a medical representative always in the hospital as queries were easily answered by telephoning Pfizer.

The complainant stated that before the two representatives left she told them of her discontent at their criticism of another company. They defended themselves and stated that they were not doing so. The complainant did not remember any apology – only embarrassed looks.

The complainant stated that it was not her practice to write complaints and had found it quite difficult, however she considered that the two representatives were using unfair tactics to put doubt into the minds of the doctors.

PANEL RULING

The Panel noted that the parties had provided differing accounts of the meeting. It was difficult in such cases to determine exactly what had transpired. A judgement had to be made on the available evidence.

The Panel noted that the representatives in question had been discussing their low molecular weight heparin, Clexane, in a hospital which used Pfizer's product Fragmin. The representatives were trying to get the hospital to change to use Aventis' product. Part of the discussion which took place involved consideration of Pfizer's local support for its product. The complainant stated that the Aventis representatives had claimed that the local Pfizer representative had been sacked in the Pfizer/Pharmacia take-over. Aventis submitted that one of its representatives had stated that Pfizer's level of representative support for Fragmin had been reduced and that its local representative no longer worked for the company. While it was not possible to determine exactly what had been said it was clear that the current decreased level of local representative support for Fragmin by Pfizer had been discussed. The Panel did not know whether the representatives had initiated this topic of conversation, nonetheless they could be seen as casting doubt upon Pfizer's ability to support the product and its commercial viability.

The Panel bore in mind that extreme dissatisfaction was necessary on the part of a complainant before he or she was moved to submit a complaint. The complainant stated that doubts had been put in the mind of at least one consultant and that the representatives had been saying the same thing to other doctors in the hospital. The Panel considered that, on balance, by discussing Pfizer's currently reduced local support for Fragmin, the Aventis representatives had failed to maintain a high standard of ethical conduct and had failed to comply with all relevant requirements of the Code. Breaches of Clauses 9.1 and 15.2 were ruled.

With regard to Clause 2 the Panel noted that a ruling of a breach of that clause was seen as a sign of particular censure. The Panel did not consider that the issue warranted such censure and so no breach of Clause 2 was ruled.

The Panel noted that Aventis had stated that its representatives had discussed the service levels that Aventis could provide if the local NHS trust changed to using its product Clexane instead of Pfizer's Fragmin. No details of this discussion were given nor was it the subject of complaint. The Panel was concerned about the impression given by this statement. Certain activities were permitted under the Code. The Panel requested that Aventis be reminded of the requirements of Clause 18.1 of the Code. Any service offered by Aventis must comply with the Code.

Complaint received **12 December 2003**

Case completed **10 February 2004**

CASE AUTH/1541/12/03 *NO BREACH OF THE CODE*

HEAD OF PRESCRIBING AND PHARMACY SERVICES v SCHERING-PLOUGH

Conduct of representative

The head of prescribing and pharmacy services to a primary care trust (PCT) complained that in a presentation to a group of practice managers one of Schering-Plough's representatives had promoted Ezetrol and Asmanex even though none of the practice managers were prescribers. The complainant was concerned that the attendees had been given misleading information; the representative had implied that there was outcome data for Ezetrol, which was not so and the representative's statement that Ezetrol was being widely prescribed was not reflected by local prescribing patterns. The representative also implied that Asmanex was approved by local specialists which was not so.

The Panel noted that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint. The Panel noted that the parties' account of events differed; it was difficult to know exactly what had transpired at the meeting in question. Although the Panel appreciated that the complainant had been very upset by the representative's presentation, it considered that there was no evidence to show that he had made unsubstantiated or exaggerated claims. On the balance of the information before it the Panel ruled no breach of the Code.

The Panel noted that the Code did not preclude administrative staff from being invited to meetings where appropriate, provided that the subject matter related to practice administration. Schering-Plough had submitted that the representative's presentation had lasted five or ten minutes and in that time he had referred to Ezetrol, Asmanex and an asthma audit. In the Panel's view there was no evidence to show that the presentation had not been tailored towards the audience. It was unlikely that the representative could have done much more than inform the practice managers of the availability of the products and service. On the balance of the information before it the Panel ruled no breach of the Code.

The Panel considered that there was no information before it to show that the representative had failed to recognise the professional standing of the audience or that his presentation was inaccurate. No breach of the Code was ruled in that regard.

The head of prescribing and pharmacy services to a primary care trust (PCT) complained about the conduct of a representative of Schering-Plough Ltd.

COMPLAINT

The complainant stated that, at a meeting for practice managers the representative had promoted prescription only medicines, Ezetrol (ezetimibe) and Asmanex (mometasone furoate), even though none of the practice managers were prescribers. The complainant was particularly concerned that the attendees had been given misleading information. This was especially disappointing as, prior to the launch of the Ezetrol and Asmanex, Schering-Plough had been told of the PCT's policy and sent copies of relevant newsletters. In particular the representative: implied that there was outcome data for Ezetrol but Schering-Plough had confirmed that this was not so; stated that 'ezetimibe is the buzz word on everyone's lips' and was being widely prescribed, which was not so as the local PCT data revealed. Local specialists had confirmed that they were not endorsing its use widely and implied that Asmanex was approved by local specialists who had confirmed that this was not so.

The complainant alleged that the following clauses had been breached for the reasons stated:

- Clause 7.4; any claim must be capable of substantiation.
- Clause 7.10; use of superlatives.
- Clause 9.2; all material and activities must recognise the professional standing of the audience to which they were directed.
- Clause 12.1; could interest in the promotional material reasonably be assumed? Material devised for clinicians might not be appropriate for administrative staff.
- Clause 15; oral representations as well as printed material needed to be accurate.
- Clause 19.1; administrative staff might be invited to meetings when the subject matter was related to practice administration.

When writing to Schering-Plough to advise it of the complaint the Authority asked, that with regard to Clause 15, the company consider Clause 15.2 in particular.

RESPONSE

Schering-Plough noted that the complaint had arisen from a ten minute presentation at a practice managers' forum. Fifteen practice managers from local surgeries, six representatives of the PCT and two representatives from the trust had attended this meeting.

The primary care development manager who had organised the meeting had invited Schering-Plough's representative to attend. His brief oral presentation comprised an overview of two medicines launched that year (Ezetrol for hypercholesterolaemia and Asmanex for asthma) and information about a recently launched, non-promotional asthma audit service. The representative strenuously denied he made any claims in breach of the Code or outside Schering-Plough's briefing and training material.

The complainant's first concern was that the representative implied that there was outcome data for Ezetrol. The representative denied making such a claim. The training material on Ezetrol, and the representatives' briefing material did not suggest that the company had such data.

Schering-Plough submitted that, with regard to the statements that 'ezetimibe was the buzz word on everyone's lips' and was being widely prescribed, again, its representative had been misquoted. The company noted that its current sales figures for Ezetrol, in particular the data showing the percentage of GPs who had prescribed it, demonstrated that it was widely prescribed.

The third concern was that the representative implied that Asmanex was approved by local specialists who had confirmed that this was not so. Schering-Plough noted, however, that a formulary application for Asmanex had been submitted. Its information was that this was endorsed, as was required, by the relevant local consultants. Further support for Asmanex came from its sales data. The PCT in question ranked high in terms of its use of Asmanex. Schering-Plough did not know which local specialists had told the complainant that Asmanex was not approved, but stated that it would be happy to supply the names of local consultants who were prescribing Asmanex.

Though not specifically stated, the complainant appeared to consider it inappropriate for the representative to inform practice managers of new products that were likely to have an impact on surgery and PCT budgets. Schering-Plough submitted that practice managers had a key role in the running of surgeries and must be classified as 'appropriate administrative staff' who should be aware of potential changes in healthcare practice.

With regard to the clauses of the Code cited by the complainant, Schering-Plough stated:

- Clauses 7.4 and 7.10 – the representative denied he had made any claims that either could not be substantiated or which made use of superlatives.
- Clause 9.2 – the representative maintained that he acted in a way that recognised the special nature of medicines and the professional nature of the audience. It was regrettable that he offended the complainant.
- Clause 12.1 – Schering-Plough was unsure as to what the complainant referred. Its representative was invited to the meeting to present. It could be assumed that this invitation reflected a level of interest in his products.
- Clause 15 – the representative denied that his oral presentation lacked 'accuracy, fairness or good taste'.
- Clause 19 – Schering-Plough noted that the supplementary information to Clause 19 stated that 'Administrative staff may be invited to meeting where appropriate. For example receptionists might be invited to a meeting in a general practice where the subject matter related to practice administration'. The company submitted that this was a practice managers' forum and that it was thus appropriate to inform practice managers of the launch of two new products that could alter prescribing habits and budgets, and of a new asthma audit program.
- Clause 15.2 – the representative denied that he had fallen short of maintaining 'a high standard of ethical conduct in the discharge of [his] duties'. His personal integrity was strongly supported by his line manager. The representative had passed the ABPI Medical Representatives Examination and this was the first complaint Schering-Plough had ever received about his conduct.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant noted that Schering-Plough's response implied that the meeting was organised by a PCT primary care development manager who invited the representative to give a presentation on the three items. This was not so. The PCT manager did not organise the meeting, she assisted practice managers in the mail out. The representative was present as the company had provided refreshments for the meeting; he had not been invited to give a presentation. The fact he did so was a surprise to those present as this was not the normal custom.

The complainant noted that the company stated that the representative had passed the ABPI Medical Representatives Examination, as though to imply this should be evidence alone that he could not act inappropriately. The complainant further noted that the representative denied making inflated claims for the products, both in terms of implying outcome data and to the extent of local use. A member of the PCT pharmacy team was present who could verify what he said and the impression this gave. In terms of the statement regarding the company's sales data, the complainant noted that, as far as she was aware, companies only had access to sales figures and not prescribing by GPs. Local PACT data bore out the veracity of her previous statement as it could be seen exactly who prescribed any medicine at any time in the area. The complainant thus assumed that the company's definition of 'widely prescribed' differed from hers.

The complainant stated that following a previous visit from Schering-Plough representatives to the PCT, when they implied they had met with local respiratory consultants who endorsed the use of Asmanex, the two consultants concerned subsequently stated that they had neither seen representatives from the company nor endorsed the use of this product. The complainant had an email to that effect. The complainant confirmed that the two consultants had not made a formulary application. If Schering-Plough believed that inclusion in a hospital formulary meant endorsement of the product in primary care, it misunderstood the process. Some products would be available in the hospital in order to treat 'difficult' patients but in primary care they might be second/third choice products or not prescribed at all. The complainant noted that the company implied that if a consultant used a product that should equal endorsement of it in the community.

The complainant reiterated that the local consultants did not endorse this product first choice in the community and the local joint prescribing guidelines demonstrated this. These guidelines were developed in conjunction with local specialists.

The complainant considered that promotion of prescription only medicines to administrative staff was inappropriate. Such staff should not be involved in the clinical decision making process. Nor were they intimately involved in managing prescribing budgets.

The complainant considered that Schering-Plough's response missed out the discourteous behaviour of the company. Staff at the PCT had taken time in their extremely busy schedule to extend a courtesy to the company by previously meeting with it to discuss Ezetrol, Asmanex and the asthma audit service. Staff had told the company their views and acquainted it with local policy. The representative in question clearly had no problem with standing up at what he thought was a PCT meeting and promoting messages which were not only contrary to local policy, but were inflated and misleading, to an audience untrained in the clinical decision making processes and who would not be able to question what he said. The complainant suspected that he was unaware there was a PCT prescribing support pharmacist in the audience.

FURTHER COMMENTS FROM SCHERING-PLOUGH

Schering-Plough stated that it had a copy of a letter on the PCT's headed paper entitled Practice Manager's Forum which listed the dates of future practice manager meetings and stated at the bottom, 'Volunteers to arrange drug reps would be welcomed'.

Schering-Plough stated that its representatives were encouraged to make appropriate presentations at meetings. In the company's view, to provide hospitality without the accompanying educational, scientific or promotional content, would not be in compliance with the Code. The company also had emails requesting that the representative in question sponsor more of these events. These requests have been received from the PCT after the meeting in question.

Schering-Plough submitted that passing of the ABPI Examination demonstrated that its representatives had fulfilled the training requirements set down by the ABPI. The company was satisfied that the representative in question had not acted inappropriately; his track record across a variety of performance parameters was very good and the company would be happy to provide evidence of these if required. It seemed that the representative was accused of implying a number of things in his presentation. To a large degree this was a matter of interpretation of the facts.

Schering-Plough stated that it had access to a number of sources of sales data which when combined gave a good representation of what was happening in that area. The PCT was ranked tenth nationally for Ezetrol sales at the time the meeting was conducted.

Schering-Plough stated that the previous meeting referred to was attended by the regional manager responsible for the area and by the hospital specialist representative. The four local respiratory consultants were seen in 2003 and this was documented. The company understood from the formulary pharmacist at one of the local hospitals that it was necessary to have the signature of all four consultants to complete a formulary application. Schering-Plough had been assured on a number of occasions by the relevant staff members at the hospital that an application had been submitted. It would not be unreasonable to assume that an application had been submitted. It would not be unreasonable to assume that an application to use the product, or for formulary status, implied a level of endorsement of it as a possible treatment option. Asmanex was neither positioned nor promoted as a first line treatment for severe asthmatics. It was a valuable alternative for use in step 2 of the British Thoracic Society Guidelines and was promoted as such. Schering-Plough would expect it to be prescribed in line with this guidance.

Schering-Plough stated that it would not subscribe to the view that it had implied that if a consultant used a product then that should equal endorsement for wider scale use in the community. The company's position was as described above. Schering-Plough was aware that consultants and GPs would see widely differing patients and that they would choose their products accordingly.

Schering-Plough submitted that the regional manager for the area in question approved many meetings in his region during 2003; only four of these were with practice managers. The company noted that the Code stated that administrative staff might attend meetings where appropriate and considered that occasionally this was appropriate and that those who ran primary care practices should be kept informed of what was happening in their area. This was particularly pertinent with the introduction of the new GP contract, where the practice manager played an integral role in the monitoring and delivery of clinical and non clinical markers.

Schering-Plough noted that this was only a five minute presentation and it considered that it was important and necessary to work in partnership with all stakeholders in the NHS, where possible.

PANEL RULING

The Panel noted that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint. The Panel noted that the parties' account of events differed; it was difficult to know exactly what had transpired at the meeting in question. Although the Panel appreciated that the complainant had been very upset by the representative's presentation, it considered that there was no evidence to show that he had made unsubstantiated or exaggerated claims. On the balance of the information before it the Panel ruled no breach of Clauses 7.4 and 7.10 of the Code.

The Panel noted that the Code did not preclude administrative staff from being invited to meetings

where appropriate, provided that the subject matter related to practice administration. Schering-Plough had submitted that the representative's presentation had lasted five or ten minutes and in that time he had referred to Ezetrol, Asmanex and an asthma audit. In the Panel's view there was no evidence to show that the presentation had not been tailored towards the audience. It was unlikely that the representative could have done much more than inform the practice managers of the availability of the products and service. On the balance of the information before it the Panel ruled no breach of Clauses 12.1 and 19.1.

The Panel considered that there was no information before it to show that the representative had failed to recognise the professional standing of the audience or that his presentation was inaccurate. No breach of Clauses 9.2 and 15.2 was ruled.

Complaint received **22 December 2003**

Case completed **10 March 2004**

CASE AUTH/1542/12/03

VOLUNTARY ADMISSION BY JANSSEN-CILAG

Evra patient website

Janssen-Cilag voluntarily advised the Authority that the print preview and printed pages of a patient website for Evra (norelgestromin and ethinyl estradiol) featured the claim 'Evra The right contraceptive choice'.

The Director of the Authority decided that as the matter related to material for patients it was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This was consistent with advice given by the Appeal Board and published in the August 1997 edition of the Code of Practice Review.

The Panel noted that the website provided women with useful information about the product and gave details of support services. The claim 'Evra The right contraceptive choice' had appeared in small print in the top left-hand corner of the web pages either when the print preview screen was viewed or when a page was printed. The Panel noted that only the screen dump version of the website had been approved by the company, Janssen-Cilag's explanation being that the website was designed for viewing on screen; the company did not expect the pages to be printed by a visitor to the site. The Panel considered that such an expectation was unreasonable and printing from the site ought to have been anticipated. The Panel considered that the claim at issue was not factual or presented in a balanced way. A breach of the Code was ruled. The Panel noted that the site was designed for women already prescribed Evra and that it was password protected. In such circumstances the site was not an advertisement to the general public. No breach of the Code was ruled. The printed pages ought to have been approved by the company.

The Panel considered that high standards had not been maintained. A breach of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved as a sign of particular censure.

Janssen-Cilag Ltd telephoned the Authority to discuss a claim that had appeared on a patient website for its once-weekly combined contraceptive transdermal patch, Evra (norelgestromin and ethinyl estradiol); the company's comments were treated as a voluntary admission.

COMPLAINT

Janssen-Cilag advised the Authority that the print preview and printed pages of a patient website for Evra featured the claim 'Evra The right contraceptive choice'.

The Director of the Authority decided that as the matter related to material for patients it was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This was consistent with advice given by the Appeal Board and published in the August 1997 edition of the Code of Practice Review.

Janssen-Cilag was asked to respond in relation to Clauses 2, 9.1, 20.1 and 20.2.

RESPONSE

Janssen-Cilag explained that the evra.co.uk website was designed as a support service for women who had been prescribed Evra. It was password protected and a health professional could give the website address to women using Evra. Women who had not been prescribed Evra would not be able to gain access to the site.

The factual information on the website related to the correct use of Evra and reflected information in the patient information leaflet or summary of product characteristics (SPC). Screen dumps of the website as seen by women accessing it were used for the copy approval process; copies were provided.

As part of the prevetting process the website was reviewed by the Advertising Unit of the Medicines and Healthcare products Regulatory Agency (MHRA) both as hard copy screen dumps and on a live test server. Any requests for changes were implemented before the website went live on 29 September 2003; a copy of relevant correspondence was provided.

The website was designed by a company with expertise in managing websites for viewing on screen. Janssen-Cilag had not anticipated, and still did not expect, that women would print any pages of the website. The words 'JC Evra The right contraceptive choice' were part of a hypertext markup language (HTML) tag used

as a page identifier by the website company. This could be seen as a small header if the page was printed or the print preview screen was viewed.

During the development of the website certain pages were copied from an existing sexual health website. The pages copied featured headers and HTML tags with the phrase 'The right contraceptive choice' which was a subheading for a section within the sexual health website. This strapline was then used as a working project title inserted into a HTML tag during development of the website, prior to approved copy being inserted and unfortunately remained when the website was moved from the internal development environment to the live website.

During thorough internal and external review the error was not spotted as these pages were not designed for printing and the company would not expect them to be printed by a visitor to the website.

As soon as Janssen-Cilag became aware of the potential for the HTML tag to be viewed it instructed the website company to change the wording to read 'Evra patient contraceptive patch information website'.

On 9 December the MHRA telephoned Janssen-Cilag to tell it that the HTML tag could be seen if three pages were printed. Immediately Janssen-Cilag instructed the website company to remove the tag. Janssen-Cilag gained assurance from the company that this had been completed on the same day. However, the company subsequently discovered that it took longer to change the HTML tag on a part of the website which was managed by a different company. The change was completed on this part of the website by 18 December.

The website company had revised its processes to ensure that this could not recur. Janssen-Cilag had also revised its review process to include additional review of printed pages in case they were printed from the print preview facility on websites in addition to reviewing screen dumps.

Janssen-Cilag had not intended women to see the phrase 'Evra The right contraceptive choice' and it had received no reports of either women or health professionals seeing this phrase. Although it acknowledged that the use of these words was inappropriate in a promotional piece or in an educational piece for women already using the product it believed that inadvertent inclusion of the phrase, which one would not expect to have been seen by visitors to the website, was inconsequential. The inclusion of this phrase in such a non-prominent position was not sufficient to make the website promotional.

Janssen-Cilag submitted that the website was not an advertisement to the general public or in breach of Clause 20.1 as only women who had already been prescribed Evra could access the website. The information provided was factual and presented in a balanced way. The website was not promotional when viewed as intended and overall the website was not promotional when printed notwithstanding the inadvertent inclusion of the phrase at question in the HTML tag. Consequently, the company denied a breach of Clause 20.2 of the Code.

Janssen-Cilag denied a breach of Clause 9.1 as it had maintained high standards with the review of materials and as soon as a potential error due to a technical issue was identified this was immediately addressed; and it did not believe that the website had brought the industry into disrepute and thus denied a breach of Clause 2.

PANEL RULING

The Panel noted that the website, which was password protected, was designed as a support service for women who had been prescribed Evra. Patients would be provided with the address by the prescriber. The Panel considered that the publication of such websites was a legitimate activity for a pharmaceutical company to undertake provided such activity was in accordance with the Code.

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 website provided women with useful information about Evra and gave details of support services available to them. The Panel noted that the claim 'Evra The right contraceptive choice' had appeared in small print in the top left-hand corner of the pages either when the print preview screen was viewed or when a page was printed. The Panel noted Janssen-Cilag's explanation that the claim was part of a working project title and had been used as a page identifier by the website company.

The Panel noted that only the screen dump version of the website had been approved by the company. The Panel noted the Janssen-Cilag's explanation that the website was designed for viewing on screen; the company did not expect the pages to be printed by a visitor to the site. The Panel considered that such an expectation was unreasonable and printing from the site ought to have been anticipated by the company.

The Panel considered that the claim at issue was not factual or presented in a balanced way. A breach of Clause 20.2 was ruled. The Panel noted that the site was designed for women already prescribed Evra and that it was password protected. In such circumstances the site was not an advertisement to the general public. No breach of Clause 20.1 was ruled. The printed pages ought to have been approved by the company.

The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

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

Proceedings commenced 22 December 2003

Case completed 27 February 2004

CASE AUTH/1543/12/03

MEDIA/DIRECTOR v JANSSEN-CILAG

Promotion of Evra

Janssen-Cilag telephoned the Authority about an article 'Evra – a patch on oral contraception?', in the Drug and Therapeutics Bulletin December 2003. In accordance with established practice this criticism of the promotion of Evra was taken up as a complaint under the Code.

The article criticized the claim 'more than 99% effectiveness and excellent compliance' and stated that there was no convincing evidence that long-term compliance was better with Evra than with a combined oral contraceptive (COC), nor on whether the patch was any more or less effective than a COC in preventing pregnancy. The article referred to two comparative studies, Audet *et al* (2001) and Hedon *et al* (2000) stating that neither was sufficiently large enough to assess the relative contraceptive efficacy of the patch and COCs. The article further alleged that a claim on the Evra patient website that the patch was 'just as effective as the contraceptive pill' was misleading and that such claims together with the website slogan 'Evra The right contraceptive choice' breached the advertising regulations.

The Panel noted that the claim 'With more than 99% effectiveness and excellent compliance …' appeared in a journal advertisement. An asterisk referred readers to a footnote 'Analysis of pooled data from 3 studies in woman < 90kg'. The efficacy claim was referenced to Zieman *et al* (2002), a *post hoc* analysis of pooled data from 3 multicentre, open-label studies (Audet *et al*; Hedon *et al*; Smallwood *et al* 2001) examining efficacy and cycle control over 6 or 13 cycles; the results showed an overall (method failure and user failure) Pearl Index (PI) over 13 cycles of 0.88 and a method failure PI of 0.7. The PI was the number of pregnancies per 100 women years ie (number of pregnancies x 1300)/number of cycles during therapy. Zieman *et al* concluded that the contraceptive efficacy of Evra was high. There was a significant association between baseline body weight and pregnancy (p< 0.001).

Section 4.2 of the Evra summary of product characteristics (SPC) stated that contraceptive efficacy might be decreased in woman weighing 90kg or more. Section 5.1 stated that only 10-20% of the variability in pharmacokinetic data could be explained by weight. Section 5.1 of the Evra SPC featured a table recording PI data from 5 separate studies; the overall PI was 0.9 and the method failure PI was 0.72.

The Panel considered that 'With more than 99% effectiveness …' was a strong unequivocal claim. It appeared that Evra was more than 99% effective in all women which was not so. Evra was significantly less effective in women ≥ 90kg. This was not made sufficiently clear. The footnote was inadequate in this regard. The claim was thus misleading, incapable of substantiation and exaggerated; breaches of the Code were ruled. These rulings were appealed by Janssen-Cilag.

The Appeal Board noted that Zieman *et al* studied a broad population of women who were +/- 35% of their ideal body weight. Women weighing >90kg made up just 3% (n=83) of the study population and 5/15 pregnancies occurred in this sub-group. Contraceptive efficacy was thus less in women weighing >90kg. In the Appeal Board's view, however, prescribers were well aware of the adverse effects associated with combined contraceptives and irrespective of any decrease in efficacy were unlikely to prescribe such medicines for women with a body mass index of more than 30 (which many would be if they weighed >90kg) due to the increased risk of venous thromboembolism. The Appeal Board further noted that in women weighing <90kg the overall PI was 0.6 and the method PI was 0.5. The Appeal Board considered that given the prescribers' knowledge of the therapy area and the PI data the claim was not unreasonable in relation to the overall findings of Zieman *et al* and was capable of substantiation. The claim was not misleading or exaggerated. The Appeal Board ruled no breaches of the Code.

The Panel did not consider that the claim 'With more than 99% effectiveness …' was comparative; the advertisement made no reference to COCs and no breach of the Code was ruled.

The Panel noted that the phrase '… and excellent compliance' was referenced to Archer *et al* (2002) which concluded that age did not affect compliance with Evra. Audet *et al* stated that a contraceptive with high compliance would be associated with an overall failure rate (method failure plus user failure) that was very similar to the method failure rate alone, as seen with the contraceptive patch 1.24 vs 0.99. A contraceptive with lower compliance would have a greater difference between the overall failure rate and the method failure rate due to more user failures as seen with the OC 2.18 vs 1.25. The mean proportion of each participant's cycles that demonstrated perfect compliance was 88.2% with the patch and 77.7% with the OC (p< 0.001). Audet *et al* concluded that applying a patch once a week for three weeks out of every four was associated with significantly better compliance than having to take a tablet every day for three weeks out of every four.

The Panel noted that the European public assessment report stated that in phase III studies the compliance in the Evra groups appeared to be higher in comparison with either Mercilon or [Logynon] indicating that compliance to the dose recommendations for Evra was at least as feasible as those for OCs. The Panel noted that the data had come from clinical trials and so was likely to be more favourable than when Evra was used generally.

The Panel was concerned that 'excellent compliance' was a strong claim. Nonetheless the Panel considered that, on balance, the claim was not misleading and was capable of substantiation; no breach of the Code was ruled. The advertisement made no reference to COCs; the claim was not comparative, no breach of the Code was thus ruled. The Panel did not consider that the phrase was exaggerated; no breach of the Code was ruled.

With regard to the claim 'just as effective as the contraceptive pill' which appeared on a patient website, the Panel considered that most readers would assume that it meant that the efficacy of Evra had been directly compared to all available OCs and that was not so. The European regulatory authorities had considered the PI for Evra to be comparable to the historical pregnancy rates of COCs in general. Evra had only been directly compared to Mercilon and [Logynon] in clinical trials.

The Panel considered that the claim 'just as effective as the contraceptive pill' was not factual or presented in a balanced way; a breach of the Code was ruled. The Panel did not consider that the claim constituted an advertisement to the public; no breach of the Code was ruled. The Panel further considered that given the audience high standards had not been maintained; a breach of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2. The rulings of breaches of the Code were appealed.

The Appeal Board noted that Evra had been directly compared to Mercilon and [Logynon] in two different head-to-head trials (Audet *et al* and Hedon *et al*). Neither trial had shown any significant differences in the PI for Evra compared with that of the comparator. A third study, Dittrich *et al* (2002), compared Evra and Cilest and showed no significant difference between the two on presumed ovulation as assessed from hormonal measurements and follicular size.

The Appeal Board noted that the European regulatory authorities had considered the PI for Evra to be comparable to the historical PIs of COCs in general.

On balance the Appeal Board considered that the claim 'just as effective as the contraceptive pill' which appeared on the patient website was factual and presented in a balanced way; no breach of the Code was ruled. The Appeal Board further considered that high standards had been maintained and no breach of the Code was ruled.

The Panel considered that its rulings in Case AUTH/1542/12/03 that the claim 'Evra The right contraceptive choice' on a patient website was not factual or presented in a balanced way and that high standards had not been maintained also applied here in Case AUTH/1543/12/03.

Janssen-Cilag Ltd telephoned the Authority about an article entitled 'Evra – a patch on oral contraception?' which appeared in the Drug and Therapeutics Bulletin December 2003. The article criticized the promotion of Evra. In accordance with established practice this criticism was taken up by the Director as a complaint under the Code.

COMPLAINT

The article in the Drug and Therapeutics Bulletin criticized the claim 'more than 99% effectiveness and excellent compliance' used in promotional material for health professionals; the article stated that there was no convincing evidence that long-term compliance was better with Evra than with a combined oral contraceptive (COC), nor on whether the patch was any more or less effective than a COC in preventing pregnancy. The article referred to two comparative studies, Audet *et al* (2001) and Hedon *et al* (2000) stating that neither trial was sufficiently large enough to assess the relative contraceptive efficacy of the patch and COCs. The article further alleged that a claim on the Evra patient website that the patch was 'just as effective as the contraceptive pill' was misleading and that such claims together with the website slogan 'Evra The right contraceptive choice' breached the advertising regulations.

Janssen-Cilag was asked to respond in relation to Clauses 7.2, 7.3, 7.4 and 7.10 with regard to promotional material aimed at health professionals and Clauses 2, 9.1, 20.1 and 20.2 with regard to the website. The complaint regarding the claim 'Evra The right contraceptive choice' had already been ruled to be in breach of Clauses 9.1 and 20.2 by the Panel in Case AUTH/1542/12/03. Janssen-Cilag had accepted these rulings and provided the requisite undertaking and assurance.

1 Claim 'With more than 99% effectiveness and excellent compliance'

RESPONSE

Janssen-Cilag provided a copy of a journal advertisement for health professionals (ref 03702) which bore the claim 'With more than 99% effectiveness and excellent compliance'. Janssen-Cilag submitted that the claim was supported by clinical data, commentary from regulatory authorities and a UK expert family planning review unit.

Janssen-Cilag stated that the efficacy of Evra had been studied in a large clinical trial programme of 3,300 women. In the analysis of pooled data Evra was shown to have an overall Pearl Index (PI) of 0.88 and a method failure PI of 0.7 (Zieman *et al* 2002) ie it was more than 99% effective at preventing pregnancy. This data was included in the summary of product characteristics (SPC) which showed an overall PI for all subjects of 0.9 and a method failure PI of 0.72. Using the total patient population gave the best estimate of efficacy. The claim was therefore consistent with the SPC.

Janssen-Cilag stated that poor compliance with contraceptive methods was a key risk factor for unplanned pregnancy and it was appropriate for the high level of compliance to be highlighted in promotional materials. In the clinical trial programme compliance or adherence to treatment was collected by means of diary cards and perfect compliance with Evra was seen in 89-91% of cycles. This was a very high level of perfect compliance compared with that found with an oral contraceptive. Published data showed significantly higher levels of perfect compliance with Evra than with a COC; 89% vs 78% (Audet *et al*), and also showed a clear trend between age and the ability of women to comply with their COCs (Archer *et al* 2002).

In the Evra clinical trial programme poor compliance with the method (Evra or COC) was significantly

associated with a higher risk of pregnancy. The unpublished data from the three phase III clinical trials showed that contraceptive efficacy was significantly better (p=0.007) in cycles with perfect dosing (PI = 0.83) compared to those with imperfect dosing (PI = 6.32) irrespective of OC or patch use. When the data was analysed by method, OC users were 6.6 times more likely to become pregnant during a non-compliant cycle as compared to a compliant cycle. For the patch, women were 3.3 times more likely to become pregnant during non-compliant cycles.

Janssen-Cilag considered the high level of compliance with Evra could fairly be described as excellent.

The claim 'With more than 99% effectiveness and excellent compliance' was an accurate, balanced and fair assessment of the data and reflected all the available evidence and was not in breach of Clause 7.2. Janssen-Cilag did not accept that the comparison with OCs was misleading and was therefore not in breach of Clause 7.3. It could be substantiated by the clinical data and so was not in breach of Clause 7.4. In addition compliance had been shown to be significantly better than the oral contraceptive in three separate studies and, as poor compliance with the method had been shown to be related to the risk of pregnancy, the claim for compliance was highly relevant and not exaggerated and hence was not in breach of Clause 7.10.

PANEL RULING

The Panel noted that the claim 'With more than 99% effectiveness and excellent compliance …' appeared in a journal advertisement (ref 03702) wherein an asterisk to the phrase 'With more than 99% effectiveness …' referred readers to a footnote at the bottom of the advertisement in a small type face which stated 'Analysis of pooled data from 3 studies in woman < 90kg'. 'With more than 99% effectiveness' was referenced to Zieman *et al*, which was a *post hoc* analysis of pooled data from 3 multicentre, open-label studies examining efficacy and cycle control over 6 or 13 cycles. Zieman *et al* gave the overall (method failure and user failure) PI over 13 cycles as 0.88 and the method failure PI as 0.7. The three studies assessed were Audet *et al*, Hedon *et al* and Smallwood *et al* (2001). The PI was defined as the number of pregnancies per 100 women years computed as (number of pregnancies x 1300)/number of cycles during therapy. Zieman *et al* concluded that the contraceptive efficacy of Evra was high. There was a significant association between baseline body weight and pregnancy (p< 0.001).

Section 4.2 of the Evra SPC stated that contraceptive efficacy might be decreased in woman weighing 90kg or more. Section 5.1 discussed relevant clinical data stating that only 10-20% of the variability in pharmacokinetic data could be explained by weight. Section 5.1 of the Evra SPC featured a Pearl Indices table recording PI data from 5 separate studies; the overall PI was 0.9 and the method failure PI was 0.72.

The Panel considered that 'With more than 99% effectiveness …' was a strong unequivocal claim. It appeared that Evra was more than 99% effective in all women which was not so. Evra was significantly less effective in women ≥ 90kg. This was not made sufficiently clear. The footnote 'Analysis of pooled data from studies in women < 90kg' was inadequate in this regard. The claim was thus misleading, incapable of substantiation and exaggerated; breaches of Clauses 7.2, 7.4 and 7.10 were ruled. These rulings were appealed by Janssen-Cilag. The Panel did not consider that the claim was comparative; the advertisement made no reference to COCs. No breach of Clause 7.3 was ruled. This ruling was not appealed.

The Panel noted that the phrase '… and excellent compliance' was referenced to Archer *et al* which concluded that age did not affect compliance with Evra and the patch was uniformly easy to use across all ages. Audet *et al* stated that a contraceptive with high compliance would be associated with an overall failure rate (method failure plus user failure) that was very similar to the method failure rate alone, as seen with the contraceptive patch 1.24 vs 0.99. A contraceptive with lower compliance would have a greater difference between the overall failure rate and the method failure rate due to more user failures as seen with the OC 2.18 vs 1.25. The mean proportion of each participant's cycles that demonstrated perfect compliance was 88.2% with the patch and 77.7% with the OC (p< 0.001). Audet *et al* concluded that applying a patch once a week for three weeks out of every four was associated with significantly better compliance than was observed with having to take a tablet every day for three weeks out of every four. The authors stated that speculation that improved compliance would result in lower typical-use contraceptive failures would need to be confirmed in future studies.

The Panel noted that the EPAR stated that in phase III studies the compliance in the Evra groups appeared to be higher in comparison with either Mercilon or [Logynon] indicating that compliance to the dose recommendations for Evra was at least as feasible as those for OCs.

The Panel noted that the compliance data had come from clinical trials and so was likely to be more favourable than when Evra was used generally.

The Panel was concerned that 'excellent compliance' was a strong claim. Nonetheless the Panel considered that, on balance, the claim was not misleading and was capable of substantiation; no breach of Clauses 7.2 and 7.4 was ruled. The advertisement made no reference to COCs; the claim was not comparative. No breach of Clause 7.3 was thus ruled. The Panel did not consider that the phrase was exaggerated; no breach of Clause 7.10 was ruled. These rulings were not appealed.

APPEAL BY JANSSEN-CILAG

In relation to the claim 'With more than 99% effectiveness …' Janssen-Cilag noted that during the development of Evra a large clinical trial programme consisting of three phase III trials was completed. An analysis of the pooled data from more than 21,000 cycles of use from the three studies had given an

overall PI for all subjects in the trials of 0.9 and a method PI of 0.72 (Evra SPC). This data included all women in the trials including those with body weight >90kg (14 stone). Janssen-Cilag submitted that these PIs were consistent with the claim 'With more than 99% effectiveness'. (A PI of 1 represented 99% effectiveness at preventing pregnancy – so a PI of <1 was more than 99% effectiveness).

In addition Zieman *et al* (which analysed the group of women who weighed <90kg) demonstrated a PI of 0.6 which Janssen-Cilag submitted substantiated the claim '…with more than 99% effectiveness'.

Janssen-Cilag noted that women weighing >90kg made up just 3% of the study population. In current UK practice it would not be expected that COCs would be prescribed to many women weighing >90kg (for women <5'8" tall this equated to a body mass index (BMI) >30 so this fell in to the WHO 3 category ie where the theoretical or proven risks usually outweighed the advantages) (Guilleband, 2004).

Janssen-Cilag submitted that the footnote 'Analysis of pooled data in women weighing <90kg' was added at the request of the Medicines and Healthcare products Regulatory Agency (MHRA) following its detailed and thorough pre-vetting of all of company promotional materials which took place before their use. This gave additional information that the efficacy reported reflected that which would be expected in the population weighing <90kg.

Janssen-Cilag submitted that the quoted efficacy figures were not misleading or exaggerated as they reflected all the available evidence and could be substantiated as it has been shown in large scale trials that Evra had a PI of <1 which represented more than 99% effectiveness. Therefore the claim 'With more than 99% effectiveness …' was not in breach of Clauses 7.2, 7.4 and 7.10.

COMMENTS FROM THE DRUG AND THERAPEUTICS BULLETIN

The Drug and Therapeutics Bulletin did not comment on Janssen-Cilag's appeal.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'With more than 99% effectiveness …' was referenced to Zieman *et al*, which was a *post hoc* analysis of pooled data from 3 multicentre, open-label studies examining efficacy and cycle control over 6 or 13 cycles, which gave the overall (method failure and user failure) PI over 13 cycles as 0.88 and the method failure PI as 0.7. The three studies assessed were Audet *et al*, Hedon *et al* and Smallwood *et al*. An asterisk referred readers to a footnote at the bottom of the advertisement which stated 'Analysis of pooled data from 3 studies in woman < 90kg'. This caveat had been included at the request of the MHRA.

Section 4.2 of the Evra SPC stated that contraceptive efficacy may be decreased in woman weighing 90kg or more. Section 5.1 of the Evra SPC featured a table recording PI data; the overall PI for Evra was 0.9 and the method failure PI was 0.72.

The Appeal Board noted that Zieman *et al* studied a broad population of women who were +/- 35% of their ideal body weight. Women weighing >90kg made up just 3% (n=83) of the study population and 5/15 pregnancies occurred in this sub-group. Contraceptive efficacy was thus less in women weighing >90kg. In the Appeal Board's view, however, prescribers were well aware of the adverse effects associated with combined contraceptives and irrespective of any decrease in efficacy were unlikely to prescribe such medicines for women with a BMI>30 (which many would be if they weighed >90kg) due to the increased risk of venous thromboembolism. The Appeal Board further noted that in women weighing <90kg the overall PI was 0.6 and the method PI was 0.5. The Appeal Board considered that given the prescribers' knowledge of the therapy area and the PI data the claim 'With more than 99% effectiveness …' was not unreasonable in relation to the overall findings of Zieman *et al* and was capable of substantiation. The claim was not misleading or exaggerated. The Appeal Board ruled no breach of Clauses 7.2, 7.4 and 7.10. The appeal on this point was successful.

2 Claim 'Just as effective as the contraceptive pill'

RESPONSE

Janssen-Cilag stated that in the section 'About Evra' on the patient website the claim appeared in the following context: 'Evra is 99% effective when used correctly – just as effective as the contraceptive pill. Evra may not work as well in women who weigh 90kg (14 stone) or more'.

It was standard practice for patient information on contraception to include information about the effectiveness of a method (Family Planning Association website). Evra had been shown to be more than 99% effective at preventing pregnancy (see above) and this information was included in the SPC. Janssen-Cilag considered that it was appropriate to include information from the SPC on the patient information website. In addition this had been qualified to give additional information about women who might not achieve this level of protection against pregnancy.

In addition the efficacy of Evra had been studied in two phase III randomised head-to-head trials with oral contraceptives (Mercilon (CONT 003) and [Logynon] (CONT 004)). The information about these trials was included in the Evra SPC. In both trials there had been no significant difference in the PI for Evra and the oral contraceptive; Audet *et al* and Hedon *et al*.

The evidence that Evra had similar efficacy in head-to-head studies with the oral contraceptive was reported in a table of data included in Section 5.1 of the SPC and reproduced overleaf.

The European regulatory authorities concluded after full review of all the available data in the European public assessment report (EPAR) that the 'Efficacy of Evra was demonstrated and appeared similar to that of the comparators'. In addition the Clinical

Pearl Indices

Study Group	*CONT-002 EVRA*	*CONT-003 EVRA*	*CONT-003 COC**	*CONT-004 EVRA*	*CONT-004 COC***	*All EVRA Subjects*
# of cycles	10,743	5,831	4,592	5,095	4,005	21,669
Overall Pearl Index (95% CI)	0.73 (0.15,1.31)	0.89 (0.02,1.76)	0.57 (0,1.35)	1.28 (0.16,2.39)	2.27 (0.59,3.96)	**0.90 (0.44,1.35)**
Method Failure Pearl Index (95% CI)	0.61 (0.0,1.14)	0.67 (0,1.42)	0.28 (0,0.84)	1.02 (0.02,2.02)	1.30 (0.03,2.57)	**0.72 (0.31,1.13)**

*: Mercilon

**: Logynon equivalent

Effectiveness Unit of the Faculty of Family Planning and Reproductive Health Care also concluded in its review of published data that 'Overall Pearl Index for the contraceptive patch was similar to that of the triphasic combined oral contraceptive pill – review of fully published clinical trials'.

When seen in the context of the password protected website for women who had already been prescribed Evra, this was not an advertisement to the general public and was therefore not in breach of Clause 20.1. The information on the website was factual and presented in a balanced way and did not raise unfounded hopes of successful treatment and therefore was not in breach of Clause 20.2 of the Code.

Janssen-Cilag submitted that the statement 'Just as effective as the contraceptive pill' was accurate, balanced and fair and reflected all the available evidence and hence not in breach of Clause 7.2; the comparison was not misleading and so not in breach of Clause 7.3 and the claim was capable of substantiation and so not in breach of Clause 7.4.

Janssen-Cilag had maintained high standards throughout and denied a breach of Clause 9.1 and denied that it had brought the industry into disrepute and denied a breach of Clause 2.

PANEL RULING

The Panel noted that comparative efficacy for a new oral contraceptive was generally determined by studying a sufficient number of menstrual cycles to give an overall PI. The Panel noted Janssen-Cilag's submission that the European regulatory authorities had concluded in the EPAR that the efficacy of Evra had been demonstrated and appeared similar to that of the comparators.

The Panel considered that most readers would assume that the claim 'just as effective as the contraceptive pill' meant that the efficacy of Evra had been directly compared to all available OCs and that was not so. The European regulatory authorities had considered the PI for Evra to be comparable to the historical pregnancy rates of COCs in general. Evra had only been directly compared to Mercilon and [Logynon] in clinical trials.

In relation to the claim 'Evra The right contraceptive choice' the Panel considered its comment and rulings in Case AUTH/1542/12/03 also applied here.

The Panel considered that both claims 'just as effective as the contraceptive pill' and 'Evra The right contraceptive choice' were not factual or presented in a balanced way; a breach of Clause 20.2 was ruled. The Panel did not consider that the claims constituted an advertisement to the public; no breach of Clause 20.1 was ruled. The Panel further considered that given the audience high standards had not been maintained; a breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved as a sign of particular censure. The rulings of breaches of the Code in respect of the claim 'just as effective as the contraceptive pill' were appealed. The rulings with regard to the claim 'Evra The right contraceptive choice' had already been accepted (Case AUTH/1542/12/03).

APPEAL BY JANSSEN-CILAG

Janssen-Cilag submitted that the claim 'Just as effective as the contraceptive pill' had to be viewed in context to allow adequate consideration. On the website it appeared as follows:

> 'Evra is 99% effective when used correctly – just as effective as the contraceptive pill. Evra may not work as well in women who weigh 90kg (14 stone) or more.'

Janssen-Cilag noted that in the Evra clinical development programme there had been three head-to-head trials (Audet *et al*, Hedon *et al*, Dittrich *et al* 2002) (one phase II and two phase III) using three different oral contraceptives. The oral contraceptives used in the trial programme were [Logynon], Mercilon and Cilest.

Janssen-Cilag noted that the contraceptives used as comparator agents all had ethinyl estradiol combined with the progestogens levonorgestrel, desogestrel or norgestimate. This selection of comparators crossed the range of second and third generation pills and monophasic and triphasic pills and reflected the range of COCs commonly used in the UK. Each study had shown no significant difference in efficacy between Evra and the oral contraceptive used.

Janssen-Cilag noted that the three formulations of COCs used as comparator agents in trials with Evra made up 25% of the UK COC market (data on file). COCs which contained any of the three progestogens used in the comparative trials either as monophasic or

triphasic COCs made up 76% of the UK market (Evra SPC). Janssen-Cilag submitted that the head-to-head comparative studies using three different agents meant that the claim 'just as effective as the contraceptive pill' was a fair reflection of the data.

Janssen-Cilag submitted that in a patient information piece it was not appropriate to state the brand names or generic names of the three different COCs that had been used in the trials so the familiar term 'the oral contraceptive' was used. The information and language used on this site for patients who had already been prescribed Evra was consistent with the type of information distributed by the family planning association, BUPA and BBC information websites which were some of the leading sources of web based information in the UK.

Janssen-Cilag submitted that women who were taking 'the pill' did not differentiate between brands; they assumed that all were very similar with respect to efficacy and there was no data to suggest that there were variations in the efficacy of the different COCs. It was therefore not relevant in this patient information to include a reference to the brand names or constituents of the oral contraceptives tested.

Janssen-Cilag submitted that it was generally accepted that COCs were 99% effective when used properly and its clinical trial programme had shown efficacy of the oral contraceptives used to be consistent with this, and Evra was also shown in the clinical trials to be 99% effective (Evra SPC).

Janssen-Cilag noted that the European regulatory authorities concluded after full review of all the available data in the EPAR, a document published by them on the European Medicines Evaluation Agency (EMEA) website, that the 'Efficacy of Evra was demonstrated and appeared similar to that of the comparators'. In addition the Clinical Effectiveness Unit of the faculty of family planning and reproductive healthcare also concluded in its review of published data that the 'Overall Pearl Index for the contraceptive patch was similar to that of the triphasic combined oral contraceptive pill – review of fully published clinical trials'.

Janssen-Cilag submitted that the claim 'just as effective as the contraceptive pill' would not lead the reader to believe that Evra had been directly compared to all available oral contraceptives as suggested in the ruling.

Janssen-Cilag submitted that as three studies had shown no significant difference in efficacy between Evra and the oral contraceptives, and the EMEA had concluded that the efficacy of Evra was similar to the comparators, then the claim 'just as effective as the contraceptive pill' was factual and in the context of the website it was presented in a balanced way and was not in breach of Clause 20.2.

Janssen-Cilag submitted that before all Evra promotional materials were distributed, including via the website, they were reviewed in full by the MHRA. Any changes suggested by the MHRA were implemented and the final versions were agreed with the MHRA. Janssen-Cilag submitted that high standards had been maintained at all times and so it was not in breach of Clause 9.1.

COMMENTS FROM THE DRUG AND THERAPEUTICS BULLETIN

The Drug and Therapeutics Bulletin did not comment on Janssen-Cilag's appeal.

APPEAL BOARD RULING

The Appeal Board noted that Evra had been directly compared to Mercilon and [Logynon] in two different head-to-head trials (Audet *et al* and Hedon *et al*). Neither trial had shown any significant differences in the PI for Evra compared with that of the comparator. A third study, Dittrich *et al* 2002, compared Evra and Cilest and showed no significant difference between the two on presumed ovulation as assessed from hormonal measurements and follicular size.

The Appeal Board noted that the European regulatory authorities had considered the PI for Evra to be comparable to the historical PIs of COCs in general.

On balance the Appeal Board considered that the claim 'just as effective as the contraceptive pill' which appeared on the patient website was factual and presented in a balanced way; no breach of Clause 20.2 was ruled. The Appeal Board further considered that high standards had been maintained and no breach of Clause 9.1 was ruled. The appeal on this point was successful.

Proceedings commenced 22 December 2003

Case completed 7 April 2004

CASE AUTH/1546/1/04

NOVO NORDISK/DIRECTOR v ORION

Breach of undertaking

Novo Nordisk alleged that the claim '9 out of 10 women on Indivina are still maintained on the lowest dose at 6 months' in an Indivina advertisement issued by Orion had previously been ruled in breach of the Code in Case AUTH/1502/8/03. 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 given previously by the Appeal Board.

The Panel noted that in Case AUTH/1502/8/03 Orion had accepted the Panel's rulings of breaches of the Code with regard to the claim '9 out of 10 women on Indivina are still maintained on the lowest dose at 6 months' and provided the requisite undertaking and assurance that the material at issue had last been used in September 2003. Turning to the case now before it, Case AUTH/1546/1/04, the Panel noted that an advertisement, containing the same claim appeared in the December 2003 edition of The Journal of the British Menopause Society. As a consequence the company had failed to comply with its undertaking. A breach of the Code was ruled.

The Panel noted Orion's submission that the product manager had spoken to the advertising agency but also noted that in written communications to each other neither Orion nor the advertising agency referred to withdrawal of material. There was no document before the Panel which showed what instructions had been issued by Orion's advertising agency to the journals. The Panel considered that Orion's efforts to ensure withdrawal of all relevant material were inadequate such that high standards had not been maintained; a breach of the Code was ruled. The Panel further considered that Orion's efforts were insufficient and brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Novo Nordisk Limited complained that an Indivina advertisement (ref HRT0931) issued by Orion Pharma (UK) Ltd, and published in the December 2003 edition of The Journal of the British Menopause Society, contained a claim which had previously been ruled in breach of the Code in Case AUTH/1502/8/03. Novo Nordisk had been the complainant in the previous case. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance given previously by the Appeal Board.

The advertisement at issue in Case AUTH/1502/8/03 bore the reference IND0794. The advertisement now at issue (HRT0931) would be covered by the ruling in Case AUTH/1502/8/03 as it included the same claim.

COMPLAINT

Novo Nordisk noted that the advertisement contained the claim '9 out of 10 women on Indivina are still maintained on the lowest dose at 6 months' which had been ruled in breach of the Code in Case AUTH/1502/8/03. A breach of Clause 22 was alleged.

In addition to Clause 22 cited by Novo Nordisk, the Authority requested Orion to consider the requirements of Clauses 9.1 and 2.

RESPONSE

Orion acknowledged that publication of the advertisement at issue was in breach of its undertaking of 16 September 2003 with regard to Case AUTH/1502/8/03 and accepted that it was therefore in breach of Clause 22 of the Code.

Orion stated that it took its obligations under the Code extremely seriously and was committed to complying with its requirements. The error which led to the publication of this advertisement appeared to have arisen at the journal itself, which used the incorrect electronic file of artwork despite having been informed by the advertising agency that the file had been withdrawn and a replacement issued.

The course of events for withdrawal of materials in order to ensure compliance with the undertaking of 16 September was as follows:

- Following the ruling that the Indivina advertisement (HRT0931) was in breach of Clauses 7.2 and 7.4 (Case AUTH/1502/8/03), Orion reviewed all Indivina materials and identified three sales force items that contained the same claim.
- During the week of 8 September 2003, the Indivina product manager wrote to all members of the sales force and identified the promotional items at issue and stated that these should no longer be used; details for their return to head office for destruction were included. Representatives were asked to sign and return an undertaking that use of these items had ceased and that they had returned all items in their possession. This process was audited to ensure that all representatives responded and all materials were recovered. The advertising agency was informed that these items were in breach and began to prepare replacements.
- During the same week the product manager spoke and wrote to the advertising agency to tell it that the Indivina advertisement HRT0931 had been ruled in breach of the Code and was not to be used again.
- The advertising agency then telephoned all journals in which advertising space had been booked to inform them that new artwork would be supplied and that the old advertisement was not to be run under any circumstances. Since the files were supplied electronically it was not possible for the agency to physically recover the artwork.
- The advertising agency prepared a new advertising schedule which included details of whether the revised artwork had been provided to the five journals in which space had been booked between 15 September and the end of 2003 when the

campaign was due to be reviewed. The advertising agency supplied the revised artwork to all five journals in time to meet their print deadlines.

- The advertisement in The Journal of the British Menopause Society in December 2003 was the final appearance of the revised artwork during 2003. It was the only Indivina advertisement booked to appear in this journal since September (the journal was a quarterly publication). The artwork was identical to that supplied and run in another journal (Practice Nurse, 14 November); it was simultaneously put on a disk (the usual format by which the agency supplied advertisements to this journal) and dispatched to meet its copy date.

Orion considered that it had taken all possible steps to ensure compliance with its undertaking of 16 September 2003. There were 13 appearances of the advertisement or an insert containing similar artwork booked between 16 September and the end of 2003; these appeared in five different journals. In all instances apart from this one, the correct artwork was used. The appearance of the advertisement that had been ruled in breach appeared to have been an error by the journal, which was not within the company's control. As already stated, the journal had been informed that the advertisement HRT0931 was not to be used and had been supplied with replacement artwork.

Orion greatly regretted that this error had occurred but it did not consider that it had breached either Clause 9.1 or Clause 2. Its actions showed that it had maintained high standards throughout and that it had taken all possible steps to ensure that the original breach was not repeated. The company did not consider that its actions brought discredit to the industry since it accepted the original breach, withdrew the advertisement promptly and issued alternative artwork, demonstrating its commitment to the Code and the undertaking it had signed.

In response to a request for further information Orion provided a copy of the email sent from the product manager to the advertising agency on 3 September 2002 and stated that as a result of this email and further telephone conversations the agency clearly understood that the revised advertisement was to be used in future. Copies of two advertising progress schedules were 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.

Case AUTH/1502/8/03 concerned the promotion of Indivina by Orion. Orion accepted the Panel's rulings of breaches of the Code with regard to the claim '9 out of 10 women on Indivina are still maintained on the lowest dose at 6 months' and provided the requisite undertaking and assurance, dated 16 September, stating that the material at issue had last been used on 12 September 2003.

Turning to the case now before it, Case AUTH/1546/1/04, the Panel noted that an advertisement, containing the same claim as had been at issue in the previous case had appeared in the December 2003 edition of The Journal of the British Menopause Society. As a consequence the company had failed to comply with its undertaking. A breach of Clause 22 was ruled. The Panel noted that Orion had accepted this point.

The Panel noted that on Wednesday, 3 September, the day after having received notification of the ruling in Case AUTH/1502/8/03, the Indivina product manager had contacted the advertising agency to inform it that the company had been ruled in breach of the Code. The email stated that there was to be a meeting to discuss the next steps ie change the claim or appeal the Panel's ruling. The materials at issue were listed as detail aid, desk top panels and advertisements. The Panel noted that the email did not identify the claim at issue, the reference numbers of the material at issue or what Orion expected the agency to do next. The email stated that there was to be a meeting two days later between Orion and the agency. The Panel noted that on the advertising agency's Orion progress schedule for the week commencing 8 September it was stated that, with regard to revised advertisements and GP inserts, the client and the agency had discussed the Panel's ruling on 5 September. The progress schedule for the week commencing 22 September showed that with regard to the advertisements, the agency was to supply revised copy to all journals during September/October 2003. There was no indication that the agency recognised that the old advertisements were to be withdrawn or had been instructed by Orion to take any action in that regard.

The Panel considered that it was incumbent upon companies to ensure that they, or their agents, gave clear instructions to all parties in the advertising/publishing chain about the withdrawal of advertisements which were in breach of the Code. The Panel noted Orion's submission that the product manager had spoken to the advertising agency. The guidelines on company procedures relating to the Code of Practice, however, stated that companies were advised to keep written records of the action taken to withdraw material. In that regard the Panel noted that in written communications to each other neither the company nor the advertising agency referred to withdrawal of material. There was no document before the Panel which showed what instructions had been issued by Orion's advertising agency to the journals. The Panel noted that amended advertisements had appeared in all but the December issue of The Journal of the British Menopause Society but nonetheless considered that Orion's efforts to ensure withdrawal of all relevant material were inadequate such that high standards had not been maintained; a breach of Clause 9.1 was ruled. The Panel further considered that Orion's efforts were insufficient and brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **8 January 2004**

Case completed **17 February 2004**

CASE AUTH/1548/1/04

GENERAL PRACTITIONER v ASTRAZENECA

Symbicort mailing

A general practitioner complained that neither a letter nor a mock newspaper, sent in a mailing on Symbicort (budesonide/eformoterol), included the non-proprietary names of the medicine next to the most prominent display of the brand name.

The Panel noted that each item contained two very obvious mentions of the name Symbicort; in the heading in plain black type and the coloured product logo in the bottom right hand corner. With regard to the letter the Panel considered that, on balance, the product logo was the most prominent display of Symbicort. The total area taken up by the product name in the logo was marginally greater than that which it took up in the heading. The colour of the logo, red and blue on a white background, added to its prominence. The non-proprietary names were incorporated into the product logo. No breach of the Code was ruled.

With regard to the mock newspaper the Panel considered that on balance the mention of Symbicort in the headline was more prominent than in the product logo. The purpose of a headline was to catch attention, added to which the total area taken up by the product name in the headline was significantly greater than that taken up by the product logo. Although the product logo was in red and blue on a light background, a colour photograph was immediately above it which detracted from it, making it less obvious. The Panel thus considered that the non-proprietary names should have appeared immediately adjacent to the mention of Symbicort in the headline. A breach of the Code was ruled.

A general practitioner complained about a Symbicort (budesonide/eformoterol) mailing sent by AstraZeneca UK Limited.

The mailing consisted of a letter (ref SYMB 03 13213A) headed 'Exciting News Symbicort and Seretide compared' and a mock newspaper (ref SYMB 03 13213B) with the headline 'Symbicort superior to Seretide in severe exacerbation control'. In the bottom right hand corner of the front page of both items was the brand logo which incorporated the non-proprietary names.

COMPLAINT

The complainant stated that on the front sheet of each item Symbicort was mentioned by name in prominent type at the top of the sheet and then in smaller type at the bottom with the approved names beneath. However the most prominent mention of the word Symbicort was not accompanied by the approved names and a breach of the Code was alleged.

In writing to AstraZeneca attention was drawn to the requirements of Clause 4.3 of the Code.

RESPONSE

AstraZeneca stated that the mailing was sent in January. The company noted the requirements of Clause 4.3 of the Code and drew attention to the phrase 'the most prominent display of the brand name'.

In certifying this item AstraZeneca decided that it was not immediately apparent that the first mention of Symbicort was the most prominent display of the brand name. Both items were colour publications where the colour scheme meant that the Symbicort logo at the bottom of each page was as prominent than [sic] the first mention of Symbicort (in black).

On that basis, AstraZeneca did not consider that the items in question were in breach of Clause 4.3 of the Code.

PANEL RULING

The Panel noted that Clause 4.3 required that the non-proprietary name of the medicine or list of active ingredients where such existed must appear immediately adjacent to the most prominent display of the brand name, in bold of a size such that a lower case 'x' was no less than 2mm in height or occupied a total area no less than that taken up by the brand name.

The Panel noted that each item contained two very obvious mentions of the name Symbicort; once in the heading to each piece, in plain black type, and the coloured product logo in the bottom right hand corner. The issue to be decided was which was the most prominent display. The definition of 'prominent' given in the New Shorter Oxford Dictionary was, *inter alia*, 'Standing out so as to catch attention; conspicuous …'. The Panel considered each item separately. With regard to the letter the Panel considered that, on balance, the product logo was more prominent than the mention of Symbicort in the heading. The total area taken up by the product name in the logo was marginally greater than that taken up by the product name in the heading. The colour of the logo, red and blue on a white background, added to its prominence. The non-proprietary names were incorporated into the product logo. No breach of Clause 4.3 was ruled with regard to the letter.

With regard to the mock newspaper the Panel considered that on balance the mention of Symbicort in the headline was more prominent than the product logo. The purpose of a headline was to catch attention, added to which the total area taken up by the product name in the headline was significantly greater than that taken up by the product logo. Although, as in the letter, the product logo was in red and blue on a light background, a colour photograph was immediately above it which detracted from it, making it less obvious. The Panel thus considered that the non-proprietary names should have appeared immediately adjacent to the mention of Symbicort in the headline. Failure to do this meant that AstraZeneca had failed to meet the requirements of Clause 4.3 and a breach of that clause was ruled with regard to the mock newspaper.

Complaint received **19 January 2004**

Case completed **25 February 2004**

CASE AUTH/1551/2/04

PFIZER and BOEHRINGER INGELHEIM v GLAXOSMITHKLINE

Promotion of Seretide

Pfizer and Boehringer Ingelheim jointly complained about the claim 'Seretide in COPD [chronic obstructive pulmonary disease]' which appeared in a Seretide detail aid and journal advertisement issued by GlaxoSmithKline. The complainants noted that Seretide was only licensed in a restricted group of COPD patients ie those with severe disease (FEV1 <50% predicted normal) and a history of repeated exacerbations, who had significant symptoms despite regular bronchodilator therapy. Further, only one of the six Seretide formulations (Seretide 500 Accuhaler) was so licensed. The complainants alleged that the claim implied that all formulations of Seretide could be used in any COPD patient which was not so.

The Panel considered that, as alleged, the claim was inconsistent with the particulars listed in the summary of product characteristics and thus was misleading with regard to the licensed indication. Breaches of the Code were ruled.

Pfizer Limited and Boehringer Ingelheim Limited complained jointly about the promotion of Seretide (salmeterol/fluticasone) in chronic obstructive pulmonary disease (COPD) by GlaxoSmithKline UK Ltd. The materials at issue were a detail aid (ref SFC/DAP/03/07422/1-FP June 2003) and an advertisement (ref SFC/FPA/03/08090/1) which had been published in Pulse, 24 November 2003. Both pieces included the product logo immediately followed by 'in COPD' such that the claim in full read 'Seretide in COPD'.

COMPLAINT

Pfizer and Boehringer Ingelheim stated that their main concern was that Seretide (a fixed dose combination of the bronchodilator, salmeterol, and the inhaled corticosteroid, fluticasone) was indicated for use in COPD in a restricted group of patients. The licensed indication was: 'Seretide (Accuhaler) 500 only: Seretide is indicated for the symptomatic treatment of patients with severe COPD (FEV1 <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy'.

Of the six Seretide formulations marketed in the UK only the Seretide 500 Accuhaler was licensed for use in COPD, and only in the sub-group of COPD patients as detailed above. All other presentations were only indicated for use in asthma.

Both the advertisement and the detail aid at issue used the bold claim 'Seretide in COPD' without qualification. A breach of Clause 3.2 was alleged. Pfizer and Boehringer Ingelheim alleged that the claim was all-embracing and implied a role for Seretide for all COPD patients, rather than the restricted group detailed in the marketing authorization.

The claim 'Seretide in COPD' implied that Seretide might be used in all doses and all formulations in COPD. The information on the dose and formulation for COPD contained in the prescribing information was insufficient to support such a claim. The prescribing information used in the detail aid and the advertisement covered asthma and COPD and all formulations, and it was easy to overlook the fact that only Seretide 500, one puff twice a day was licensed for COPD, and at no point was it made clear that this dose was only available in the Accuhaler.

Nothing in the detail aid qualified the claim 'Seretide in COPD', although the front page contained a footnote referring the reader to the prescribing information on the back cover. Reference to the whereabouts of the prescribing information could not be regarded as sufficient qualification. Moreover the supplementary information to Clause 7 of the Code specifically warned against the qualification of general claims by the use of footnotes. The detail aid would be used by a representative who would not necessarily tell the health professional that the prescribing information was on the back cover. A breach of Clause 7.2 was alleged.

RESPONSE

GlaxoSmithKline noted that there had been extensive inter-company dialogue regarding the promotion of Seretide in COPD. The company had already agreed with the complainants that it would amend its materials without an admission of a breach of the Code. GlaxoSmithKline submitted that in its previous communications with both parties, it had consistently stated that it considered that its promotion of Seretide in COPD had always been within the terms of its licence and had not been misleading. The company considered this to be the case, because:

- All of its promotional materials were subject to pre-vetting and approval by the Medicines and Healthcare products Regulatory Agency (MHRA) following extensive discussion. The MHRA approved the use of the material in question in May 2003, and thus agreed that it reflected the approved licence for Seretide in COPD. The MHRA was the reference member state for the application in Europe for the licence in COPD.
- All the information contained within the advertisement and detail aid clearly showed the patient population for which Seretide in COPD was licensed and was referenced accordingly. In addition, the indication was also clearly stated and as part of the briefing material, clearly and regularly reinforced.

- Clear and accurate prescribing information, guiding the health professional in their decisions, was provided.

GlaxoSmithKline submitted that it had promoted Seretide in COPD within its licensed indication at all times; it had actively participated in the pre-vetting process with the MHRA, clearly referenced all of its materials and provided thorough briefing for its representatives. The company denied that it had breached Clauses 3.2 and 7.2.

PANEL RULING

The Panel noted that only the Seretide 500 Accuhaler was indicated for the symptomatic treatment of COPD and only then in patients with severe disease (FEV1 < 50% predicted normal) and a history of exacerbations, who had significant symptoms despite regular bronchodilator therapy (ref summary of product characteristics (SPC)). The Panel considered, however, that the claim 'Seretide in COPD' implied that all formulations of Seretide could be used in any patient with COPD and this was not so. The Panel considered that the claim was inconsistent with the particulars listed in the Seretide SPC and thus misleading with regard to the licensed indication. Breaches of Clauses 3.2 and 7.2 of the Code were ruled.

Complaint received **9 February 2004**

Case completed **16 March 2004**

CASE AUTH/1552/2/04 *NO BREACH OF THE CODE*

PRIMARY CARE TRUST CHIEF PHARMACIST v SANOFI-SYNTHELABO

Depakote dosing card

The chief pharmacist to a primary care trust complained that a Depakote dosing card, issued by Sanofi-Synthelabo, was particularly distasteful. The front page featured a photograph which appeared to be taken by a person standing on a ledge of a tall building and looking downwards. The photographer's shoes were in the foreground with the road some distance below. The headline read 'I'm on top of the world' followed by 'G Evans, aged 32 Acute Mania sufferer (untreated)'. The card had been found lying around within a public area of a hospital.

The Panel noted that the same dosing card was at issue in a previous case, Case AUTH/1537/11/03, where, in relation to an allegation that the image stigmatised the condition, the Panel had noted, *inter alia*, the therapeutic area (acute treatment of a manic episode associated with bipolar disorder) and Sanofi-Synthelabo's submission that patients in need of such treatment often displayed high-risk behaviours which could lead to tragic consequences. The situation depicted was one in which a patient with bipolar disorder might find themselves and was thus relevant to Depakote's licensed indication. In the Panel's view the majority of health professionals would not find the image shocking. The Panel considered that in the context in which it was used the image was not unreasonable in relation to the requirements of the Code. No breach of the Code was ruled.

Turning to the present case, Case AUTH/1552/2/04, the Panel noted that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to submit a complaint. Although the Panel appreciated that the complainant had found the image distasteful it did not consider that the majority of health professionals would. The Panel noted Sanofi-Synthelabo's submission that the image had been shown to psychiatrists prior to its adoption none of whom had objected to it. The Panel thus considered that the image was not unreasonable in relation to the requirements of the Code. No breach of the Code was ruled.

The Panel noted that the dosing card, intended for health professionals, had been found by the complainant in a public area of a hospital. Whilst the Panel noted that the dosing card had been distributed within hospitals by representatives there was no evidence to indicate that either the representative or the company had made it available to members of the public. No breach of the Code was ruled in that regard.

The chief pharmacist to a primary care trust complained about the promotion of Depakote (valproate semisodium) by Sanofi-Synthelabo Limited. The material at issue was a 4 page dosing card (ref DEP-03/024) the front page of which featured a photograph which appeared to be taken by a person standing on a ledge of a tall building and looking downwards. The photographer's shoes were in the foreground with the road some distance below. The headline read 'I'm on top of the world' followed by 'G Evans, aged 32 Acute mania sufferer (untreated)'.

The dosing card had been the subject of a similar complaint, Case AUTH/1537/11/03, wherein the Panel had ruled no breach of the Code. Paragraph 5.1 of the Constitution and Procedure provided that complaints closely similar to previous ones should normally proceed if the previous complaint involved a decision of the Code of Practice Panel which was not the subject of appeal to the Code of Practice Appeal Board. The previous case was not the subject of an appeal and the Director therefore decided that this complaint should proceed in the normal way.

COMPLAINT

The complainant was concerned that the dosing card, which she and others found particularly distasteful,

was found lying around within a public area of a hospital.

When writing to Sanofi-Synthelabo the Authority asked it to respond in relation to Clauses 9.1, 9.2, 20.1 and 2 of the Code.

RESPONSE

Sanofi-Synthelabo stated that the image of the shoes on top of a building had been used on a detail aid, dosage card and a mailing but not in journal advertising. The 'shoes' campaign had been used exclusively in materials for health professionals and was not intended for use with members of the general public. The purpose of the material was to highlight the importance of bipolar disorder, a condition for which awareness, even amongst the medical community, was relatively low. The majority of patient groups would agree with Sanofi-Synthelabo that there was a great need for more attention to be drawn to this much-neglected condition. This need to raise awareness underlaid the use of such high impact imagery in the promotional campaign; the dosage card needed to be viewed within that context.

Patients experiencing manic episodes associated with bipolar disorder were often extremely impulsive and displayed high-risk behaviours. Such behaviour could lead to tragic consequences and the use of such imagery to highlight the negative aspects of a condition should give rise to a greater understanding of the difficulties faced by some patients.

Sanofi-Synthelabo confirmed that its salesforce used this card with psychiatrists to highlight the dosing schedule of Depakote. Depakote was one of the available treatments for mania, and given the risks that mania presented, the advertisement sought to advocate its early, more widespread use at appropriate doses.

During the development and subsequent approval of the campaign the 'shoes' image was shown to groups of psychiatrists prior to its adoption; at no stage were any concerns raised as to the suitability of this image in depicting mania. The company accepted that the image was powerful, but it was not its view that the image itself was likely to cause offence to psychiatrists, as they were very familiar with such high-risk behaviours commonly exhibited by their patients. The image was designed to link such high-risk behaviour, which was commonly associated with other mental illnesses, with a manic episode. It was possible to view the euphoria associated with mania in a positive light and not fully appreciate the associated dangers.

The image deliberately contrasted the patient's euphoria with the clear and present risk he was in due to his position on top of the world. He might be euphoric and in his exhilarated state was looking down on the world below oblivious to the risk he had placed himself in. The image quite graphically displayed the danger that existed from being figuratively on top of the world.

The dosing card was not intended to be viewed by the public. Sanofi-Synthelabo took this matter very seriously and had contacted the local representative who stated that at no time did he give or witness the dosage card being given to a member of the public. Sanofi-Synthelabo did not know how the material in question was left where a patient could view it. It was possible that a health professional received this card from one of the company's representatives and left it where members of the public could view it. Sanofi-Synthelabo would rebrief the salesforce of the need to ensure that materials were not left in view of patients. Should it become aware of any such activity in contravention of the Code, it would ensure appropriate steps were taken to address the important matter.

The 'shoes' campaign was intended to raise awareness of the serious nature and consequences of bipolar disorder. It was intended to encourage health professionals to engage in the management of patients and raise awareness of the impulsive and high-risk behaviours often demonstrated by patients experiencing a manic episode.

Sanofi-Synthelabo noted the ruling of no breach of the Code in Case AUTH1537/11/03, but stated that in light of the present and previous complaints, it would voluntarily withdraw any materials bearing this image.

PANEL RULING

The Panel noted that the same dosing card was at issue in the previous case, Case AUTH/1537/11/03 where, in relation to an allegation that the 'shoes' image stigmatised the condition the Panel had noted, *inter alia*, the therapeutic area and Sanofi-Synthelabo's submission that patients experiencing manic episodes associated with bipolar disorder often displayed high-risk behaviours which could lead to tragic consequences. The situation depicted was one in which patients with bipolar disorder might find themselves and was thus relevant to Depakote's licensed indication. In the Panel's view the majority of health professionals would not find the image shocking. The Panel considered that in the context in which it was used the 'shoes' image was not unreasonable in relation to the requirements of Clauses 9.1 and 9.2 of the Code. No breach of those clauses was ruled.

Turning to the present case, Case AUTH/1552/2/04, the Panel noted that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to submit a complaint. Although the Panel appreciated that the complainant had found the 'shoes' image distasteful it did not consider that the majority of health professionals would. The Panel noted Sanofi-Synthelabo's submission that the image had been shown to psychiatrists prior to its adoption none of whom had objected to it. The Panel thus considered that the image was not unreasonable in relation to the requirements of Clauses 9.1 and 9.2 of the Code. No breach of Clauses 9.1 and 9.2 was ruled.

The Panel noted that the dosing card, intended for health professionals, had been found by the complainant in a public area of a hospital. Whilst the Panel noted that the dosing card had been distributed within hospitals by representatives there was no

evidence before the Panel to indicate that either the representative or the company had made it available to members of the public. No breach of Clauses 20.1 and 2 was ruled.

The Panel noted that as a result of the two complaints about the suitability of the 'shoes' image Sanofi-Synthelabo had voluntarily decided to withdraw the relevant material regardless of the Panel's rulings.

Complaint received **13 February 2004**

Case completed **11 March 2004**

CASE AUTH/1553/2/04

MEDIA/DIRECTOR v PFIZER

Promotion of Vfend

An article entitled 'Caspofungin and voriconazole for fungal infections' in the Drug and Therapeutics Bulletin, January 2004, criticized Pfizer's use of the claim 'Significantly improved survival compared to amphotericin B' in the promotion of Vfend (voriconazole). In accordance with established procedure the matter was taken up by the Director as a complaint under the Code.

The article referred to the results of a 12-week, non-blinded trial of 391 immunocompromised patients, aged 12 years or over, with definite or probable invasive aspergillosis randomised to voriconazole or amphotericin B (Herbrecht *et al* 2002). The median duration of treatment was 77 days for voriconazole and 10 days for amphotericin B. The primary outcome measure was the number of patients achieving a complete or partial response. In the 277 patients with confirmed invasive aspergillosis at baseline, there was a significant difference in survival rates at 12 weeks in favour of voriconazole (70.8% v 57.9%). The article noted that this result was the basis of the claim in question but queried the robustness of the study given the duration and because the data were derived from a subgroup analysis (ie 71% of randomized patients) of a secondary outcome measure (survival rate). The article thus concluded that there was no convincing published evidence to justify the claim that voriconazole 'Significantly improved survival in invasive asperigillosis compared to amphotericin B'.

The Panel noted that the primary endpoint of Herbrecht *et al* was to demonstrate the non-inferiority of Vfend versus amphotericin B at week 12 in the predefined modified intent to treat (MITT) population ie those patients who had received one dose of assigned study medication and had a baseline diagnosis of definite or probable invasive aspergillosis. Duration of survival in the two groups up to week 12 was one of the secondary outcome measures. The two groups were well matched and there were no significant differences in the demographic characteristics between the (intent to treat) ITT population and the MITT population. The MITT population was thus a statistically and clinically valid population.

The Panel noted that at week 12 the survival rates were 70.8% (Vfend) and 57.9% (amphotericin B) in the MITT population. Herbrecht *et al* stated that similar results were observed in the ITT population. The Panel did not consider that the fact that survival was a secondary endpoint alone detracted from the robustness of the result. The survival endpoint was predefined and the superior result not isolated; Vfend was also superior for the primary and the two other secondary endpoints.

The study authors concluded overall that in the highly immunosuppressed patients enrolled in the study initial therapy with Vfend proved superior to initial therapy with amphotericin B. Food and Drug Administration (FDA) data on file referred to by Pfizer discussed the same data set and provided further details of the study. Overall the authors concluded that Kaplan-Meier plots showed an early and continued survival benefit in favour of Vfend.

Section 5.1 of the Vfend summary of product characteristics (SPC) described the Herbrect data and stated, *inter alia*, that a satisfactory global response was seen in 53% of voriconazole treated patients compared to 31% of patients treated with amphotericin B. The SPC further stated the 84-day survival rate for Vfend was statistically significantly higher than that for amphotericin B and a clinically and statistically significant benefit was shown in favour of Vfend for, *inter alia*, time to death. The relevant section referred to patients with poor prognosis.

The Panel considered that the claim 'Significantly improved survival compared to amphotericin B' was strong and unequivocal but noted that the audience would be familiar with the difficulty of treating systemic fungal infections. The Panel noted that the claim 'Superior success and survival rates in invasive aspergillosis compared with amphotericin B' appeared as a discrete bullet point on the outside back cover of the detail aid beneath the heading 'Reasons to prescribe Vfend'. No further details of the study were provided on that page. On an inside page of the detail aid and of one of the leavepieces a graph depicting survival rates over 12 weeks appeared immediately below the claim. In the other leavepiece the claim *per se* did not appear but the graph showing the results did. This leavepiece included the claim 'This study shows the superiority of [Vfend] over amphotericin B as initial therapy for invasive aspergillosis in terms of response rate, survival rate and safety'. On balance, and despite the intended audience and the additional information provided about the study on the pages of the detail aid and leavepiece described above, the

Panel considered the claim at issue implied that Vfend-treated patients had more chance of surviving, and recovering, than if treated with amphotericin B whereas the data was limited to only showing the position at 12 weeks. The claim could not stand alone. The Panel thus considered that the claim was not adequately supported by the study as alleged; breaches of the Code were ruled.

An article entitled 'Caspofungin and voriconazole for fungal infections' in the Drug and Therapeutics Bulletin, January 2004, criticized the promotion of Vfend (voriconazole) by Pfizer Limited. In accordance with established procedure the matter was taken up by the Director as a complaint under the Code.

Vfend, a broad spectrum antifungal agent was indicated, *inter alia*, for the treatment of invasive aspergillosis.

COMPLAINT

The article referred to a claim that voriconazole 'Significantly improved survival in invasive asperigillosis compared to amphotericin B' and, *inter alia*, discussed the clinical efficacy of voriconazole in invasive aspergillosis. The article referred to the results of a 12-week, non-blinded trial of 391 immunocompromised patients, aged 12 years or over, with definite or probable invasive aspergillosis randomised to voriconazole or amphotericin B (Herbrecht *et al* 2002). Patients unresponsive or intolerant to therapy could be treated with other antifungal medicines and was more likely in the amphotericin B group. Fewer patients in the amphotericin B group had definite invasive aspergillosis at baseline. The median duration of treatment was 77 days for voriconazole and 10 days for amphotericin B. The primary outcome measure was the number of patients achieving a complete or partial response. Analysis at week 12 showed more of the voriconazole treated patients had achieved the primary outcome measure of complete or partial response (49.7% v 27.8%). In the 277 patients with confirmed invasive aspergillosis at baseline, there was a significant difference in survival rates at 12 weeks in favour of voriconazole (70.8% v 57.9%). The article noted that this finding appeared to be the basis for Pfizer's claim of improved survival with voriconazole compared with amphotericin B but queried the robustness of the study given the duration of initial, non-blinded treatment between voriconazole and amphotericin B, and because the data were derived from a subgroup analysis (ie 71% of randomized patients) of a secondary outcome measure (survival rate). The article thus concluded that there was no convincing published evidence to justify the claim that voriconazole was superior to amphotericin B at increasing survival rates in patients with invasive aspergillosis.

When writing to Pfizer the Authority asked it to respond in relation to Clauses 7.2, 7.3 and 7.4 of the Code.

RESPONSE

The claim 'Significantly improved survival compared with amphotericin B' was used in Pfizer's current Vfend campaign and in previous materials; the claim had not changed significantly in presentation or emphasis since Vfend was launched in September 2002. Two leavepieces (refs VFE 408 and VFE 409) and a detail aid (ref VFE 417) bore the claim at issue.

The supporting data came primarily from Herbrecht *et al* which was the largest prospective, randomised, comparative trial ever conducted in the treatment of invasive aspergillosis. The clear conclusions of the study were that Vfend was superior to amphotericin B as initial therapy for invasive aspergillosis, in terms of response rates, survival rates and safety.

Pfizer explained that aspergillosis was a life-threatening fungal infection which primarily occurred in patients with prolonged neutropenia and in transplant recipients. It was notoriously difficult to diagnose and treatment was associated with generally poor outcomes. Clinical trials in this setting were always complex in design, reflecting the challenging clinical setting, patient characteristics, the routine use of add-on/salvage therapy, as well as the high morbidity and mortality rates. The final design of Herbrecht *et al* culminated from a collaboration between Pfizer, the European Organisation for Research and Treatment of Cancer (EORTC) and an independent international steering committee. Pfizer sponsored the study which was carried out to international standards of good clinical practice. The conduct of the study and data review were overseen by three independent expert boards and the data were held and analysed by both Pfizer and EORTC.

Pfizer noted that full details of the study design and methods were given in a schematic representation in the detail aid. The primary endpoint of the study was non-inferiority of response rates for Vfend compared with amphotericin B at week 12 in the predefined modified intent to treat (MITT) population. Secondary endpoints included superiority of response at the end of initial therapy, comparison of safety and survival at week 12.

Pfizer noted that successful outcomes at 12 weeks in the MITT group were 76/144 (52.8%) for Vfend-treated patients as opposed with 42/133 (31.6%) in amphotericin B-treated patients. The absolute difference was 21.2% with a 95% confidence interval for the difference being 10.4-32.9. The conclusions of the study clearly demonstrated the clinical superiority of Vfend over amphotericin B. In addition, retrospective subgroup analysis appeared to demonstrate that Vfend was superior in most subgroups including the intention to treat (ITT) group. The demonstration of superiority in both MITT and ITT groups, plus the subsequent subgroup analyses added considerable weight to the robust nature of the superiority result. Survival rates at week 12 (a predefined secondary endpoint) were 70.8% for the Vfend-treated group and 57.9% in the amphotericin B-treated group. This difference was statistically significant with a hazard ratio of 0.59 (95% CI 0.4-0.88). Herbrecht *et al* concluded that 'This study showed the superiority of voriconazole over amphotericin B as initial therapy for invasive aspergillosis, in terms of response rate, survival and safety'.

Vfend was granted a marketing authorization in March 2002 following a centralised EU procedure. Therapeutic indications included the treatment of invasive aspergillosis and Section 5.1 of the summary of product characteristics (SPC) included the following description of Herbrecht *et al*: 'The 84 day survival rate for voriconazole was statistically significantly higher than that for the comparator and a clinically and statistically significant benefit was shown in favour of voriconazole for both time to death and time to discontinuation due to toxicity'.

Whilst Herbrecht *et al* formed the supporting data for the superiority and improved survival claims Pfizer also noted that Food and Drug Administration (FDA) data on file and Boucher *et al* (2003) were further analyses of the same dataset and Steinbach *et al* (2003) was a retrospective review of outcomes for patients treated for invasive aspergillosis caused by *Aspergillus terreus*, a resistant form of aspergillosis with a high mortality.

Pfizer was concerned that its promotion of Vfend had been criticised by the Drug and Therapeutics Bulletin. The company believed it had demonstrated that this criticism was unjustified and that its promotional claims were supported by both high quality peer reviewed data and regulatory review. Pfizer denied any breaches of Clauses 7.2, 7.3 and 7.4 of the Code.

In response to a request for further information Pfizer stated that the detail aid had been distributed to haematologists, microbiologists, and intensive care physicians. Leavepiece VFE408 had been distributed to haematologists and leavepiece VFE409 had been distributed to microbiologists.

PANEL RULING

The Panel noted that the primary endpoint of Herbrecht *et al* was to demonstrate the non-inferiority of Vfend versus amphotericin B at week 12 in the MITT population. Secondary outcome measures were to compare the duration of survival in the two groups up to week 12, safety, and to demonstrate the superiority of the response to Vfend at the end of the initial therapy in the MITT population.

The Panel noted that the survival data were based on the MITT population, a predefined primary efficacy population comprising patients who had received one dose of assigned study medication and had a baseline diagnosis of definite or probable invasive aspergillosis. The two groups were well matched and there were no significant differences in the demographic characteristics between the ITT population and the MITT population. The MITT population was thus a statistically and clinically valid population.

The Panel noted that at week 12 the survival rates were 70.8% (Vfend) and 57.9% (amphotericin B) in the MITT population. Herbrecht *et al* stated that similar results were observed in the ITT population. The Panel did not consider that the fact that survival was a secondary endpoint alone detracted from the robustness of the result. The survival endpoint was predefined and the superior result not isolated; Vfend was also superior for the primary and the other two secondary endpoints.

The Panel noted that the median duration of treatment for Vfend was 77 days and that for amphotericin B was 10 days; some patients could not tolerate amphotericin B and had to be switched to other licensed antifungal therapy. The study authors noted that duration of treatment was unlikely to be the only factor contributing to the better overall results.

Overall, the study authors concluded that in the highly immunosuppressed patients enrolled in the study initial therapy with Vfend proved superior to initial therapy with amphotericin B.

The Panel also noted Steinbach *et al*, Boucher *et al* and the FDA data on file referred to by Pfizer. The latter discussed the same data set and provided further details of the study published as Herbrecht *et al*. The between-group difference in survival through day 84 from start of treatment in the MITT population was a predefined secondary endpoint. The authors stated that Vfend was associated with a survival advantage compared with amphotericin B. The difference in survival between the two arms showed a hazard ratio of 0.6. No p values were provided in the text or accompanying figure. Overall the authors concluded that Kaplan-Meier plots showed an early and continued survival benefit in favour of Vfend; this treatment effect was seen across both studies and in all analysis populations and in patients with poor prognostic factors.

The Panel also noted that Section 5.1 of the Vfend SPC described the Herbrecht data in 277 immunocompromised patients treated for 12 weeks stating, *inter alia*, that a satisfactory global response was seen in 53% of voriconazole-treated patients compared to 31% of patients treated with the comparator (amphotericin B). The SPC further stated the 84-day survival rate for Vfend was statistically significantly higher than that for the comparator and a clinically and statistically significant benefit was shown in favour of Vfend for, *inter alia*, time to death. The relevant section referred to patients with poor prognosis.

The Panel noted that the article which gave rise to the complaint alleged that the analysis in the MITT population and duration of treatment in Herbrecht *et al* meant such that the claim 'Significantly improved survival compared to amphotericin B' was not substantiated.

The Panel considered that the claim 'Significantly improved survival compared to amphotericin B' was strong and unequivocal but noted that the detail aid and leavepieces in which it appeared were distributed to an audience which would be familiar with the difficulty of treating systemic fungal infections. The health professionals reading the material would know that such infections were associated with a high mortality rate. The Panel noted that the claim 'Superior success and survival rates in invasive aspergillosis compared with amphotericin B' appeared as a discrete bullet point on the outside back cover of the detail aid beneath the heading 'Reasons to prescribe Vfend'. No further details of the study were provided on that page. On page 11 of the detail aid and on page 2 of one of the leavepieces (ref VFE

409) a graph depicting survival rates over 12 weeks appeared immediately below the claim. In the other leavepiece (ref VFE 408) the claim *per se* did not appear but the graph showing the results did. This leavepiece included the claim 'This study shows the superiority of [Vfend] over amphotericin B as initial therapy for invasive aspergillosis in terms of response rate, survival rate and safety'. On balance, and despite the intended audience and the additional information provided about the study on the pages of the detail aid and leavepiece described above, the Panel considered the claim at issue implied that Vfend-treated patients had more chance of surviving, and recovering, than if treated with amphotericin B whereas the data was limited to only showing the position at 12 weeks. The claim could not stand alone. The Panel thus considered that the claim was not adequately supported by the study as alleged; breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

Proceedings commenced 17 February 2004

Case completed 13 April 2004

CASE AUTH/1554/2/04

HOSPITAL PHARMACIST v AMGEN

Aranesp journal advertisement

A hospital pharmacist complained that by referencing 'Rapid and meaningful [haemoglobin] response within 4 weeks' to a paper entitled '[Aranesp] Administered Every 2 Weeks Alleviates Anemia in Cancer Patients Receiving Chemotherapy', Amgen was promoting Aranesp (darbepoetin alfa) for use once a fortnight rather than once a week as licensed. The complainant alleged that this was misleading; using Aranesp every two weeks meant that the initial dose was higher and so a more rapid response would be expected. Although the overall dose might be lower than that licensed, the effect of front loading was bound to increase the early response.

The Panel noted that the paper cited in support of the claim 'Rapid and meaningful [haemoglobin] response within 4 weeks' reported primarily upon part B of a dose- and schedule-finding study in which Aranesp, at various doses, was given every two weeks. Part A of the same study had evaluated a range of weekly doses of Aranesp and although that part of the study was described in another paper the results were reported in the one cited in the advertisement. Thus although the title of the paper, which was quoted in full in the references given in the advertisement, referred solely to the use of Aranesp every two weeks, the paper itself did not and contained the results with regard to weekly dosing upon which the claim was based. Nonetheless by quoting the title thus it appeared that the claim was based upon the use of Aranesp every two weeks which was misleading as alleged. The Panel did not consider that the sub-heading beneath which the claim appeared, 'Only Aranesp corrects anaemia with one weekly dose in a broad range of chemotherapy patients', was sufficient to negate this impression. A breach of the Code was ruled.

The Panel noted that the title of the paper referred to an unlicensed dosage schedule. The Panel considered that titles of references needed to comply with the Code when they were quoted in promotional material. Although the summary of product characteristics (SPC) referred to dosing every two weeks this was within the context of pharmacokinetics ie mean peak concentration, and not clinical use *per se*. The Panel considered that by quoting the title of the paper attention had been drawn to the use of Aranesp every two weeks; such use was inconsistent with the particulars listed in the SPC. A further breach of the Code was ruled.

A hospital pharmacist complained about the promotion of Aranesp (darbepoetin alfa) by Amgen Limited. The material at issue, an advertisement published in Hospital Pharmacist, February 2004, promoted Aranesp for the treatment of anaemia in patients receiving chemotherapy.

COMPLAINT

The complainant noted the claim 'Rapid and meaningful Hb [haemoglobin] response within 4 weeks' was referenced to Glaspy and Tchekmedyian (2002) which was entitled 'Darbepoetin Alfa Administered Every 2 Weeks Alleviates Anemia in Cancer Patients Receiving Chemotherapy'. The complainant alleged that a claim based on a dose administered fortnightly rather than the weekly dose licensed in the UK was misleading. Administering Aranesp every two weeks meant that the initial dose was higher and so a more rapid response would be expected. Although the overall dose might be lower than that licensed, the effect of front loading was bound to increase the early response. The complainant asked the Authority to investigate these misleading claims.

When writing to Amgen the Authority requested that it consider the requirements of Clauses 3.2 and 7.2 of the Code.

RESPONSE

Amgen stated that although the title of Glaspy and Tchekmedyian referred only to fortnightly dosing, the study had included weekly dosing in the design. Although it had predominantly outlined the results of dosing every two weeks, the study was also the primary reference for the results of mean haemoglobin change after 4 weeks for weekly dosing of Aranesp and thus supported the claim at issue. The study demonstrated that Aranesp dosed at 2.25mg/kg weekly produced a clinically meaningful rise in the mean haemoglobin of 0.7g/dl within 4

weeks, compared to 0.3g/dl for the epoetin alfa comparator group. Amgen therefore, submitted that the reference was appropriate, and supported the claim. As such, it was not in breach of Clause 7.2 of the Code.

With reference to Clause 3.2, Amgen considered that the use of Glaspy and Tchekmedyian was in accordance with the terms of its marketing authorization, and was consistent with the summary of product characteristics (SPC). Although the dose frequency listed in Section 4 of the SPC was weekly, fortnightly dosing was discussed in Section 5. Glaspy and Tchekmedyian looked at dosing of Aranesp both weekly and fortnightly. Both were discussed in the SPC. There was no promotion of fortnightly dosing in the advertisement, therefore Amgen did not consider that there was a breach of Clause 3.2 of the Code.

PANEL RULING

The Panel noted that the paper by Glaspy and Tchekmedyian, 'Darbepoetin Alfa Administered Every 2 Weeks Alleviates Anemia in Cancer Patients Receiving Chemotherapy', cited in support of the claim 'Rapid and meaningful Hb response within 4 weeks' reported primarily upon part B of a dose- and schedule-finding study in which Aranesp (3, 5, 7 and 9µg/kg bodyweight) was dosed every two weeks. Part A of the same study had evaluated a range of weekly doses of Aranesp and although that part of the study was described elsewhere (Glaspy *et al* 2002) the results were reported in Glaspy and Tchekmedyian. Thus although the title of Glaspy and Tchekmedyian, which was quoted in full in the references given in the advertisement, referred solely to the use of Aranesp every two weeks the paper itself did not and contained the results with regard to dosing every week upon which the claim was based. Nonetheless by quoting the title thus it appeared that the claim was based upon the use of Aranesp every two weeks which was misleading as alleged. The Panel did not consider that the sub-heading beneath which the claim appeared, 'Only Aranesp corrects anaemia with one weekly dose in a broad range of chemotherapy patients', was sufficient to negate this impression. A breach of Clause 7.2 was ruled.

The Panel noted that the title of the Glaspy and Tchekmedyian paper referred to an unlicensed dosage schedule. The Panel considered that titles of references needed to comply with the Code when they were quoted in promotional material. Although the SPC referred to dosing every two weeks this was within the context of pharmacokinetics ie mean peak concentration, and not clinical use *per se*. The Panel considered that by quoting the title of the paper attention had been drawn to the use of Aranesp every two weeks; such use was inconsistent with the particulars listed in the SPC. A breach of Clause 3.2 was ruled.

Complaint received **19 February 2004**

Case completed **29 March 2004**

CASE AUTH/1555/2/04

PRIMARY CARE TRUST v LUNDBECK

Ebixa mailing

A prescribing subcommittee at a primary care trust (PCT) alleged that a mailing sent by Lundbeck, which promoted the use of Ebixa (memantine) for the treatment of Alzheimer's disease, was inappropriate as it did not contain the advice from the summary of product characteristics (SPC) that 'treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's disease'. It appeared that Ebixa could be prescribed by any clinician regardless of experience in the diagnosis and treatment of Alzheimer's disease.

A letter, which formed part of the mailing, acknowledged that the reader could be waiting for the publication of the National Institute of Clinical Excellence (NICE) guidance in May 2005 before making a decision about whether to recommend that Ebixa be endorsed locally and noted that many patients would deteriorate significantly in the interim. Clinical data was discussed beneath the heading 'Why wait to allow the Ebixa benefits'. The accompanying booklet adopted a similar theme.

The Panel noted that Ebixa was indicated for the treatment of patients with moderately severe to severe Alzheimer's disease. Section 4.2 of the SPC stated that 'Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia'. In the Panel's view this statement was a note of caution.

The Panel noted that the description of those who could initiate and supervise treatment with Ebixa was not mentioned in any of the items at issue. The Panel noted that the mailing had been sent to NHS personnel with an interest in and responsibility for determining prescribing guidance and decisions. In the Panel's view it was important that the limitations on who could prescribe Ebixa was brought to the attention of these people so that they could issue correct prescribing guidance. The booklet had also been sent to a group of health professionals selected by Lundbeck, including 416 primary care physicians who had requested further information on Ebixa on two occasions. The Panel did not accept Lundbeck's submission that such a group could be considered compliant with the requirements of the SPC. Even though some of the recipients might have been physicians experienced in the diagnosis and treatment of Alzheimer's dementia the Panel considered that it was important that the practicalities of prescribing Ebixa were clearly stated.

Overall the Panel considered that the failure to describe those who could initiate and supervise treatment, namely physicians experienced in the diagnosis and treatment of Alzheimer's dementia, meant that the material at issue was inconsistent with the particulars listed in the SPC and thus not in accordance with the terms of the Ebixa marketing authorization. A breach of the Code was ruled. The material at issue gave the impression that any doctor could prescribe Ebixa and that was not so. The material was misleading in this regard; a breach of the Code was ruled.

A prescribing subcommittee at a primary care trust (PCT) complained about a mailing for Ebixa (memantine) sent by Lundbeck Ltd. Ebixa was indicated for the treatment of patients with moderately severe to severe Alzheimer's disease. The mailing comprised a letter headed 'A year is a long time in Alzheimer's disease' (ref 0903/EBI/511/007LN) and a concertina style booklet (ref 0903/EBI/511/007M).

The letter acknowledged that the reader could be waiting for the publication of the National Institute of Clinical Excellence (NICE) guidance in May 2005 before making a decision about whether to recommend that Ebixa be endorsed locally and noted that many patients would deteriorate significantly in the interim. Clinical data was discussed beneath the heading 'Why wait to allow the Ebixa benefits'. The booklet adopted a similar theme; one side of the opened out item featured a calendar which ran from January 2004 to May 2005; the other side discussed, *inter alia*, clinical data.

COMPLAINT

The complainant stated that the theme of the campaign was 'Why wait to prescribe' and alleged that the mailing, which had been widely distributed to primary care clinicians, was inappropriate as it did not contain the advice that was in the summary of product characteristics (SPC) that 'treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's disease'. Further the implication was that Ebixa was suitable for any clinician to prescribe regardless of experience in the diagnosis and treatment of Alzheimer's disease.

When writing to Lundbeck the Authority asked it to respond in relation to Clauses 3.2 and 7.2 of the Code.

RESPONSE

Lundbeck explained that the mailing had been sent to a targeted group of NHS personnel with an interest and responsibility for prescribing guidance and decisions, which affected groups of doctors and patients. These included pharmaceutical advisers, prescribing leads, heads of primary care, PCT Chairs, clinical governance leads and trust/PCT medical directors.

The individuals were selected because they had responsibility for determining prescribing policy in PCTs and hospital trusts and needed to be aware of recent product developments. The material was not targeted at this audience in their capacity as individual prescribers but rather to inform their decision-making concerning the prescribing policy for dementia treatments. Lundbeck had always intended that Ebixa should be prescribed by those with experience in the diagnosis and treatment of Alzheimer's dementia.

The booklet had also been sent to a selected and relevant group of NHS health professionals and prescribers (hospital pharmacists, hospital doctors (only specialist neurologists and old age psychiatrists) and primary care physicians). Of this group only 416 were primary care physicians (1% of the primary care physicians in the UK) who had received the SPC at the launch of the product and had then indicated on two separate occasions that they had a special interest in the management of dementia and would like further information on Ebixa and Alzheimer's disease, which had subsequently been sent to them. Once again they had the opportunity to request further information and the ones who had indicated the need for further information were sent the booklet.

Lundbeck submitted that this was an appropriate group to receive the booklet and such a group could be considered to be compliant with the requirements of the SPC.

Lundbeck therefore strongly denied any breach of the Code and submitted that Ebixa had been promoted in accordance with its marketing authorization and that prescribers had not been misled.

PANEL RULING

The Panel noted that Ebixa was indicated for the treatment of patients with moderately severe to severe Alzheimer's disease. Section 4.2 of the SPC stated that 'Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia'. In the Panel's view this statement was a note of caution.

The Panel noted that the description of those who could initiate and supervise treatment with Ebixa was not mentioned in any of the items at issue. The Panel noted Lundbeck's explanation that the mailing had been sent to NHS personnel with an interest and responsibility for determining prescribing guidance and decisions. In the Panel's view it was important that the limitations on who could prescribe Ebixa was brought to the attention of these people so that they could issue correct prescribing guidance. The booklet had also been sent to a group of health professionals and prescribers selected by Lundbeck of whom 416 were primary care physicians who had requested further information on Ebixa on two occasions. The Panel did not accept Lundbeck's submission that such a group could be considered compliant with the requirements of the SPC. In any event some of the recipients were pharmacists who would not be able to prescribe Ebixa. Even though some of the recipients might have been physicians experienced in the diagnosis and treatment of Alzheimer's dementia the Panel considered that it was important that the practicalities of prescribing Ebixa were clearly stated.

Overall the Panel considered that the failure to describe those who could initiate and supervise treatment, namely physicians experienced in the diagnosis and treatment of Alzheimer's dementia meant that the material at issue was inconsistent with the particulars listed in the SPC and thus not in accordance with the terms of the Ebixa marketing authorization. A breach of Clause 3.2 was ruled. The material at issue gave the impression that any doctor could prescribe Ebixa and that was not so. The material was misleading in this regard. A breach of Clause 7.2 was ruled.

Complaint received **19 February 2004**

Case completed **1 April 2004**

CASE AUTH/1558/3/04

MEDIA/DIRECTOR v ASTRAZENECA

Promotion of Symbicort

An article in the Drug and Therapeutics Bulletin entitled 'Are Seretide and Symbicort useful in COPD?' [chronic obstructive pulmonary disease] criticized the promotion of Symbicort (budesonide plus formoterol) by AstraZeneca. The article noted promotional claims for Symbicort included benefits of reducing symptoms and improving quality of life. The article reviewed the results of two randomised, double-blind, placebo-controlled trials (Szafranski *et al* 2003, Calverley *et al* 2003) and concluded that there was conflicting evidence about whether Symbicort improved quality of life, and that it did not appear to improve total symptom scores more than formoterol alone. The authors considered that this was at odds with advertising claims.

The Panel noted that Szafranski *et al* assessed the efficacy and safety of Symbicort in the management of COPD (n=812). All therapy except terbutaline was withdrawn during a two week run-in period after which patients were assigned to one of four groups – Symbicort, budesonide, formoterol or placebo. The published paper showed that only the awakening score at 12 months showed a statistically significant advantage in favour of Symbicort compared with formoterol alone but an authors' correction published some time later reported that, contrary to the original report, there was also a statistically significant difference in total symptom score at 12 months in favour of Symbicort compared with formoterol. Symbicort-treated patients had a statistically significantly improved health related qualify of life compared with placebo but no significant differences for Symbicort vs its monocomponents was reported.

Calverley *et al* assessed maintenance therapy in COPD patients (n=1,022) who had received optimal treatment (formoterol and oral prednisolone daily and terbutaline PRN) for two weeks before entry into the trial. Patients were randomised to one of four treatment groups, Symbicort, budesonide, formoterol and placebo. With regard to total symptom score Symbicort was not significantly better than either of its monocomponents alone. With regard to the mean change over 12 months in the components of the total symptom score (shortness of breath, chest tightness, cough and night-time awakening) Symbicort showed no advantage over formoterol alone and the only advantage over budesonide alone was with regard to shortness of breath. With regard to quality of life score all active treatments improved total score vs placebo, with the greatest improvement occurring with Symbicort.

The Panel noted that a number of quality of life claims had been made in various materials; the Panel considered each claim separately.

The Panel noted that the claim 'Symbicort improved patients' [quality of life impact score] by 4.7 compared with placebo' accurately reflected Szafranski *et al*. Both Szafranski *et al* and Calverley *et al* had consistently shown quality of life benefits for Symbicort vs placebo. Each time the claim was used it was clear that the comparison was with placebo. Further, a difference of 4 or more in the score represented a clinically relevant difference for the patient. The Panel did not consider that the claim was either misleading or that it was not capable of being substantiated. No breach of the Code was ruled.

The Panel noted that the claim 'Symbicort significantly reduced all symptom scores within the first week of treatment, compared with eformoterol' referenced to Szafranski *et al* was immediately followed by a second claim 'The reduction in total symptom score was sustained over 12 months' which headed a graph showing the mean change in total symptom score from baseline at 12 months for Symbicort (–2.22), formoterol (–1.95), budesonide (–1.52) and placebo (–1.45). The second claim was referenced to data on file which had been taken from the Szafranski data and was followed by '(Sum of shortness of breath, cough, chest tightness and night-time awakenings score)'.

The Panel questioned the clinical significance of the one week data of Symbicort vs formoterol given the chronic nature of COPD and the fact that the reduction in each of the separate symptom scores was not maintained over time. The Panel considered that by referring to 'all symptom scores' in the first claim and following it by a claim which referred to the total symptom score the claims together implied that in all ways Symbicort relieved symptoms more than formoterol at one week and that that advantage was maintained over one year which was not so. At 12 months there was no statistically significant difference between Symbicort and formoterol alone with regard to shortness of breath, cough or chest tightness. The claims did not reflect the evidence clearly. The Panel considered that the claims as presented were misleading and could not be substantiated. Breaches of the Code were ruled.

The Panel considered that the claim 'Symbicort significantly reduces symptom scores compared to placebo' implied that with regard to reducing all symptom scores Symbicort was better than placebo in all COPD patients. The Panel noted that the claim accurately reflected the findings of Szafranski *et al*, to which it was referenced. However, Calverley which was the larger study had shown that there was no statistically significant difference between Symbicort and placebo with regard to cough at 12 months. The Panel considered that the balance of the evidence was such that it was unclear whether Symbicort reduced cough in COPD. The Panel thus considered that the claim was misleading and could not be substantiated. Breaches of the Code were ruled.

The Panel noted that the Prescriber 'Current Thinking' supplement 'The role of Symbicort (budesonide/eformoterol) in the management of COPD' discussed COPD in general and also included an article specifically detailing the use of Symbicort. A section on symptomatic improvement

featured a graph showing the improvement in total symptom score in the first week of treatment with Symbicort vs its monocomponents (p<0.001 Symbicort vs placebo, budesonide, formoterol). The data was from Szafranski *et al*. The Panel again questioned the clinical relevance of one week data given the chronic nature of COPD. The supplement stated that 'This significant improvement [at one week] in all symptom scores was sustained over 12 months by Symbicort compared with budesonide alone and placebo'. The Panel noted its comments above with regard to the claim 'Symbicort significantly reduces symptom scores compared to placebo', Calverley *et al* had shown no statistically significant difference with regard to cough scores at 12 months between Symbicort and either of its monocomponents. The Panel thus considered that the section on symptomatic improvement was misleading in this regard and could not be substantiated. Breaches of the Code were ruled.

There was also a subsection on quality of life which discussed the results of Szafranski *et al*. It was clearly stated that the results were with regard to the comparison between Symbicort and placebo. In that regard the Panel noted its comments above relating to the claim 'Symbicort improved patients' [quality of life impact score] by 4.7 compared with placebo'. No breaches of the Code were ruled.

The Panel noted that the strapline 'Reducing symptoms. Improving quality of life. You've got it in one' appeared on an exhibition panel and two journal advertisements. The Panel noted that the left-hand side of the exhibition panel discussed the reduction in the rate of severe exacerbations with Symbicort vs its monocomponents. It was also stated that compared with formoterol Symbicort prolonged time to first exacerbation. The right-hand side of the panel discussed quality of life data vs placebo (Szafranski *et al*). The strapline ran along the bottom of the panel and would thus be read as applying to Symbicort vs placebo and each of its monocomponents. The Panel noted, however, that neither Szafranski *et al* nor Calverley *et al* had shown quality of life differences for Symbicort vs formoterol. With regard to symptoms Szafranski *et al* had shown an advantage at 12 months for Symbicort vs formoterol in total score and awakening but not for shortness of breath, cough or chest tightness. Calverley showed no differences in symptoms at one year between Symbicort and formoterol. Given the context in which it appeared ie on a panel which referred to a comparison of Symbicort and formoterol the Panel considered that the strapline was misleading and could not be substantiated. Breaches of the Code were ruled.

With regard to the advertisements the Panel noted that neither of them referred to any medicine other than Symbicort. The Panel thus considered that the strapline would be read as a comparison between Symbicort and no treatment. In that context the Panel considered that the straplines were not misleading and that they could be substantiated. No breaches of the Code were ruled.

The Panel noted that the claim 'Symbicort provide [sic] another step forward in disease management and the potential for an enhanced quality of life for COPD patients' appeared in an advertorial which discussed the benefits of Symbicort therapy vs formoterol with regard to severe exacerbations. The claim appeared immediately after that discussion and before a bar chart showing that Symbicort significantly prolonged the time to first severe exacerbation compared with formoterol. The Panel considered that in the context of which it appeared the claim implied that Symbicort improved patients' quality of life more than formoterol which was not so. Use of the phrase 'the potential for' did not negate this impression. The Panel considered that, given its context, the claim was misleading and could not be substantiated. Breaches of the Code were ruled.

An article entitled 'Are Seretide and Symbicort useful in COPD?' in the Drug and Therapeutics Bulletin, March 2004, criticized the promotion of Symbicort (budesonide plus formoterol) by AstraZeneca UK Limited. In accordance with established procedure the matter was taken up by the Director as a complaint under the Code.

COMPLAINT

The article noted that Symbicort had recently been licensed for the symptomatic treatment of patients with chronic obstructive pulmonary disease (COPD) and a history of repeated exacerbations. Promotional claims for Symbicort included benefits of 'reducing symptoms' and 'improving quality of life'. The article reviewed the results of two randomised, double-blind, placebo-controlled trials, lasting 12 months, which compared the efficacy of Symbicort with budesonide or formoterol alone, all taken via a dry-powder inhaler (Szafranski *et al* 2003, Calverley *et al* 2003).

The article noted that Szafranski *et al* compared two inhalations of budesonide 200mcg plus formoterol 6mcg alone or placebo, all taken twice daily in the treatment of moderate to severe COPD (n = 812). Primary outcome measures were the number of severe exacerbations and FEV1. Secondary outcomes related to quality of life measures. At the end of the study mean exacerbation rates were lower with Symbicort than with formoterol alone (p=0.043) or placebo (p=0.035) but not lower than with budesonide alone (p=0.385). Symbicort increased mean FEV1 15% more than budesonide alone (p<0.001) but only 1% more than formoterol alone (p=0.487). Health-related quality of life was evaluated using the St George's Respiratory Questionnaire (SGRQ) in which a reduction of 4 points from baseline was considered a relevant benefit to the patient. No benefit of this size was achieved with any treatment. Although total symptom scores improved more with the combination treatment than with budesonide alone or placebo, the difference in scores between the combination inhaler and formoterol alone were only significant within the first week of treatment.

Calverley *et al* compared two inhalations of Symbicort with budesonide 200mcg alone, formoterol 6mcg alone or placebo all taken twice daily, in patients with severe COPD (n = 1,022). The primary outcome measures of time to first exacerbation and change in

post-medication FEV1 showed statistically significant advantages for Symbicort compared with all other groups. Secondary outcome measures related to quality of life. Health-related quality of life was evaluated using the SGRQ. The combination inhaler reduced the SGRQ score by 4.5 compared with budesonide alone (p=0.014), 3.4 compared with formoterol alone (p=0.014) and 7.5 compared with placebo (p<0.001). Total symptom scores fell more with either the combination or formoterol alone than with placebo, but there was no difference between the combination inhaler and formoterol alone.

In conclusion the authors noted that there was conflicting evidence about whether Symbicort improved quality of life, and that it did not appear to improve total symptom scores more than formoterol alone. The authors considered that this was at odds with advertising claims.

When writing to AstraZeneca the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code.

RESPONSE

AstraZeneca noted that the Drug and Therapeutics Bulletin article referred to conflicting published evidence about Symbicort in COPD. This was not the case. There had been two 12-month studies looking at Symbicort treatment in patients with moderate to severe COPD. These studies had different designs. Szafranski *et al* included patients who had been withdrawn from previous therapy before randomisation in order to measure/compare improvements in COPD outcomes from therapy between products. Calverley *et al* included patients whose therapy was optimised before randomisation in order to measure/compare the maintenance in COPD outcomes or otherwise from therapy. These two different study designs were accepted in the clinical arena as providing a robust body of evidence for the use of Symbicort in this population. AstraZeneca stated that it would not expect studies of differing designs to give identical results. They would give different results to be viewed in the context of their respective study designs.

AstraZeneca noted that the claim 'Symbicort improved patients' quality of life SGRQ impact score by a clinically significant 4.7 compared with placebo' appeared in five items to be used in primary or secondary care. The claim was referenced to Szafranski *et al* in which Symbicort was shown to improve quality of life score by 4.7 compared to placebo. An improvement of 4 units on the SGRQ was clinically relevant for COPD patients and applied to the total and impact scores. This claim specified that this was a comparison with placebo. Calverley *et al* also showed that Symbicort improved SGRQ quality of life score by 7.5 vs placebo. Where the claim 'Improving quality of life' appeared in isolation Szafranski *et al* and Calverley *et al* were provided as references. In summary AstraZeneca stated that the quality of life claims were substantiated by the available evidence and were not misleading. The company denied breaches of Clauses 7.2 and 7.4 of the Code.

The claim 'Symbicort significantly reduced all symptom scores within the first week of treatment, compared with eformoterol' appeared in two items to be used in primary and secondary care. The claim was referenced to Szafranski *et al* which showed that Symbicort reduced all symptom scores within the first week of treatment vs formoterol, budesonide and placebo (p<0.05).

The claim 'Reduction in total symptom score was sustained over 12 months' appeared in the same items as above. No claim was made relative to reduction vs formoterol. When the material was developed, the claim was referenced to data on file, which was created from the Szafranski study. The information was from the original paper that showed that there was a non-significant difference for total symptom score between Symbicort and formoterol at 12 months. A significant difference was seen for Symbicort vs budesonide and placebo (p<0.001). The non-significant difference was made clear on the graph that accompanied the claim. An authors' correction published later amended the error in the 12-month scores to show a significant improvement for Symbicort vs formoterol (p=0.043). The promotional material which contained this claim was being updated to reflect the most up-to-date evidence this correction provided. Where the claim 'reducing symptoms' appeared in isolation Szafranski *et al* was provided as reference.

The claim 'Symbicort significantly reduces symptom scores compared to placebo' appeared in a journal advertisement. The claim was referenced to Szafranski *et al* and an abstract by Jones and Stahl (2003) which showed that Symbicort improved symptom scores compared to placebo (p<0.05). The claim specifically stated that it was compared to placebo. AstraZeneca stated that in summary these claims were an accurate reflection of the data when they were made. Corrections to the original data provided evidence of a statistically significant improvement for Symbicort vs formoterol for total symptom scores at 12 weeks. This up-to-date evidence was currently being incorporated into materials.

AstraZeneca did not consider that the items in question were in breach of Clauses 7.2 or 7.4 of the Code.

AstraZeneca noted that a supplement in the journal Prescriber referred to both symptomatic improvement and quality of life. This article presented the evidence in a clear and specific manner and was supported by the references outlined above.

In summary, AstraZeneca considered that the claims made regarding symptom scores and quality of life reflected an accurate, balanced, fair, objective, unambiguous and up-to-date evaluation of the evidence and were capable of substantiation and were not misleading. Any perceived conflict in data might be due to the fact that there were two different study designs. The results from the two studies needed to be interpreted taking this into account. Therefore, the comments from the Drug and Therapeutics Bulletin needed to be assessed in that context.

PANEL RULING

The Panel noted that Szafranski *et al* assessed the efficacy and safety of budesonide/formoterol (Symbicort) in the management of COPD patients (n=812) from whom all therapy except terbutaline had been withdrawn during a two week run-in period. At the end of the run-in patients were assigned to one of four groups – Symbicort (n=208), budesonide (n=198), formoterol (n=201) or placebo (n=205). Patients used daily diary cards to record morning and evening symptoms (shortness of breath, cough, chest tightness and night-time awakenings) and a health status questionnaire, the SGRQ, was completed at baseline and at 6 and 12 months. With regard to symptoms the published paper reported no statistically significant difference in total symptom score for Symbicort vs formoterol at 12 months (p=0.103). Of the components of the total symptom score only the awakening score at 12 months showed a statistically significant advantage in favour of Symbicort compared with formoterol alone (p=0.019); with regard to shortness of breath, cough and chest tightness there was no significant difference between the two treatments (p=0.107, 0.204 and 0.678 respectively). There was, however, an error in the 12-month total symptom score in the original paper and an authors' correction published some time later reported that there was in fact a statistically significant difference in favour of Symbicort compared with formoterol (p=0.043). The other values stayed the same. With regard to the SGRQ mean reductions from baseline were –3.9 and –3.6 for Symbicort and formoterol respectively. A change of 4 points from baseline was considered an important difference relevant to the patient. Compared with placebo, Symbicort significantly improved SGRQ total score (mean difference 3.9, p=0.009) and symptom (mean difference 5.9, p<0.001) and impact (mean difference 4.7, p=0.006) domains. No significant differences for Symbicort vs its monocomponents were reported.

Calverley *et al* assessed maintenance therapy in COPD patients (n=1,022) who had received optimal treatment (formoterol 9mcg bd and oral prednisolone 30mg od daily and terbutaline 500mcg as needed) for two weeks before entry into the trial. Patients were randomised to one of four treatment groups, Symbicort (n=254), budesonide (n=257), formoterol (255) or placebo (n=256). As in Szafranski *et al* patients completed daily diary cards to record symptoms of COPD and SGRQs were completed at recruitment, randomisation and at 6 and 12 months. With regard to total symptom score Symbicort was not significantly better than either of its monocomponents alone. With regard to the mean change over 12 months in the components of the total symptom score (shortness of breath, chest tightness, cough and night-time awakening) Symbicort showed no advantage over formoterol alone. The only advantage at 12 months over budesonide alone was with regard to shortness of breath. The SGRQ total score fell from baseline by a mean 4.5 units during the run-in period. During the treatment period total scores fell further by approximately 3 units in the Symbicort group and were more or less maintained by formoterol and budesonide. All active treatments improved total score versus placebo, with the greatest improvement occurring with Symbicort (differences at 12 months of –7.5, –3.0 and –4.1 vs placebo for Symbicort, budesonide and formoterol respectively). The differences between Symbicort and its monocomponents were thus –4.5 for budesonide and –3.4 for formoterol. The Panel noted that the difference between Symbicort and formoterol (<4) was thus not one which was of clinical relevance to a patient.

The Panel noted that AstraZeneca had supplied a number of Symbicort items which included a number of claims relating to quality of life. The Panel considered each claim separately.

'Symbicort improved patients' quality of life SGRQ impact score by 4.7 compared with placebo'. This claim appeared in a detail aid (ref SYMB 03 12732B), an exhibition panel (ref SYMB 03 12019), an opportunity handler (ref SYMB 03 12128) and a COPD motivator (ref SYMB 03 12737A). A closely similar claim appeared in a leavepiece (ref SYMB 03 13245 12/03).

The Panel noted that the claim accurately reflected one of the findings of Szafranski *et al*. Both Szafranski *et al* and Calverley *et al* had consistently shown quality of life benefits for Symbicort versus placebo. The Panel considered that each time the claim was used it was clear that the comparison was with placebo. Further, a difference of 4 or more in SGRQ score represented a clinically relevant difference for the patient. The Panel did not consider that the claim was either misleading or that it was not capable of being substantiated. No breach of Clauses 7.2 and 7.4 was ruled.

'Symbicort significantly reduced all symptom scores within the first week of treatment, compared with eformoterol'. This claim was referenced to Szafranski *et al* and appeared in the detail aid and the opportunity handler. In each case it was immediately followed by a second claim **'The reduction in total symptom score was sustained over 12 months'** which headed a graph showing the mean change in total symptom score from baseline at 12 months for Symbicort (–2.22), formoterol (–1.95), budesonide (–1.52) and placebo (–1.45). The second claim was referenced to data on file which the Panel noted had been taken from the Szafranski data and was followed by '(Sum of shortness of breath, cough, chest tightness and night-time awakenings score)'.

The Panel noted that total symptom score was the sum of four different scores, ie those for awakening, shortness of breath, cough and chest tightness. At one week there were statistically significant advantages for Symbicort compared to formoterol, budesonide and placebo with regard to total symptom score and each of its four components. Although in the correction of the symptom data published by Szafranski *et al*, Symbicort also statistically significantly improved total symptom scores more than formoterol, budesonide or placebo at 12 months (p<0.001) the corresponding data for the components of that score were not so positive with regard to the one year comparison with formoterol. At 12 months the only scores to show a statistically significant

advantage for Symbicort vs formoterol was for awakening (p=0.019) and for total symptoms (p=0.043). The Panel questioned the clinical significance of the one week data of Symbicort vs formoterol given the chronic nature of COPD and the fact that the reduction in each of the separate symptom scores was not maintained over time. The Panel considered that by referring to 'all symptom scores' in the first claim and following it by a claim which referred to the total symptom score the claims together implied that in all ways Symbicort relieved symptoms more than formoterol at one week and that that advantage was maintained over one year which was not so. At 12 months there was no statistically significant difference between Symbicort and formoterol alone with regard to shortness of breath, cough or chest tightness. The claims did not reflect the evidence clearly. The Panel considered that the claims as presented were misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

'Symbicort significantly reduces symptom scores compared to placebo'. This claim appeared as a discreet stabpoint in a journal advertisement which was presented as an advertorial (ref 12340).

The Panel considered that the claim implied that with regard to reducing all symptom scores Symbicort was better than placebo in all COPD patients. The Panel noted that the claim accurately reflected the findings of Szafranski *et al*, to which it was referenced. Calverley, however, had shown that there was no statistically significant difference between Symbicort and placebo with regard to cough score at 12 months (p=0.18). Although the difference between Symbicort and placebo had been statistically significant with regard to cough at 12 months (p=0.002) in Szafranski *et al*, this was a smaller study (n=812) than Calverley *et al* (n=1,022). The Panel considered that the balance of the evidence was such that it was unclear whether Symbicort reduced cough in COPD. The Panel thus considered that the claim was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

Prescriber 'Current Thinking' supplement 'The role of Symbicort (budesonide/eformoterol) in the management of COPD' (ref SYMB 03 12082). This supplement discussed COPD in general and also included an article specifically detailing the use of Symbicort in COPD. A section on symptomatic improvement featured a graph showing the improvement in total symptom score in the first week of treatment with Symbicort vs its monocomponents (p<0.001 Symbicort vs placebo, budesonide, formoterol). The data was from Szafranski *et al*.

The Panel again questioned the clinical relevance of one week data given the chronic nature of COPD. The supplement stated that 'This significant improvement [at one week] in all symptom scores was sustained over 12 months by Symbicort compared with budesonide alone and placebo'. The Panel noted its comments above with regard to the claim 'Symbicort significantly reduces symptom scores compared to placebo'. Calverley *et al* had shown no statistically significant difference with regard to cough scores at 12 months between Symbicort and either of its monocomponents. The Panel thus considered that the section on symptomatic improvement was misleading in this regard and could not be substantiated. Breaches of Clauses 7.2 and 7.4 was ruled.

There was also a subsection on quality of life which discussed the results of Szafranski *et al*. It was clearly stated that the results were with regard to the comparison between Symbicort and placebo. In that regard the Panel noted its comments above relating to the claim 'Symbicort improved patients' quality of life SGRQ impact score by 4.7 compared with placebo'. No breach of Clauses 7.2 and 7.4 was ruled.

'Reducing symptoms. Improving quality of life. You've got it in one'. This strapline appeared on an exhibition panel (ref SYMB 03 12019) and two journal advertisements (refs SYMB 03 11907 and SYMB 03 11908).

The Panel noted that the left-hand side of the exhibition panel discussed the reduction in the rate of severe exacerbations with Symbicort vs its monocomponents. It was also stated that compared with formoterol Symbicort prolonged time to first exacerbation. The right-hand side of the panel discussed quality of life data vs placebo (Szafranski *et al*). The strapline ran along the bottom of the panel and would thus be read as applying to Symbicort vs placebo and each of its monocomponents. The Panel noted, however, that although both Szafranski *et al* and Calverley *et al* had shown quality of life advantages for Symbicort vs placebo, neither had shown a difference for Symbicort vs formoterol. With regard to symptoms Szafranski *et al* had shown an advantage at 12 months for Symbicort vs formoterol in total score and awakening but not for shortness of breath, cough or chest tightness. Calverley showed no differences in symptoms at one year between Symbicort and formoterol. Given the context in which it appeared ie on a panel which referred to a comparison of Symbicort and formoterol the Panel considered that the strapline was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

With regard to the advertisements the Panel noted that neither of them referred to any medicine other than Symbicort. The Panel thus considered that the strapline would be read as a comparison between Symbicort and no treatment. In that context the Panel considered that the straplines were not misleading and that they could be substantiated. No breach of Clauses 7.2 and 7.4 was ruled.

'Symbicort provide [sic] another step forward in disease management and the potential for an enhanced quality of life for COPD patients'. This claim appeared in the advertorial.

The Panel noted that the advertorial discussed, *inter alia*, the benefits of Symbicort therapy vs formoterol with regard to severe exacerbations. The claim in question appeared immediately after that discussion and before a bar chart showing that Symbicort significantly prolonged the time to first severe exacerbation compared with formoterol (p<0.01). The Panel considered that in the context of which it appeared the claim implied that Symbicort improved

patients' quality of life more than formoterol which was not so. Use of the phrase 'the potential for' did not negate this impression. The Panel considered that, given its context, the claim was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

Proceedings commenced 5 March 2004

Case completed 20 April 2004

CODE OF PRACTICE REVIEW – MAY 2004

Cases in which a breach of the Code was ruled are indexed in **bold type**.

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1525/10/03	**Pierre Fabre v Aventis Pharma**	**Taxotere folder**	**Breach Clause 3.2**	**Appeal by respondent**	**Page 11**
1527/10/03	**GlaxoSmithKline v AstraZeneca**	**e-mail relating to the SUND study**	**Breaches Clauses 3.2, 4.1, 4.6, 7.2, 7.3, 7.4, 9.9 and 14.1**	**No appeal**	**Page 15**
1533/10/03	**Servier v Takeda**	**Actos journal advertisement**	**Breach Clause 3.2 Two breaches Clause 7.2**	**No appeal**	**Page 20**
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1548/1/04	**General Practitioner v AstraZeneca**	**Symbicort mailing**	**Breach Clause 4.3**	**No appeal**	**Page 49**
1551/2/04	**Pfizer and Boehringer Ingelheim v GlaxoSmithKline**	**Promotion of Seretide**	**Breach Clauses 3.2 and 7.2**	**No appeal**	**Page 50**
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1558/3/04	**Media/Director v AstraZeneca**	**Promotion of Symbicort**	**Five breaches Clause 7.2 Five breaches Clause 7.4**	**No appeal**	**Page 60**

PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, about seventy non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Nicholas Browne QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).

May 2004