PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 46 NOVEMBER 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.

New publication for health professionals, NHS managers, etc

The Authority and the ABPI have issued a new publication, Guidance notes for health professionals on the Code. The guidance is a brief summary of key points to help health professionals and managers understand the Code and its operation. Copies are available on the website (pmcpa.org.uk) and from the ABPI (020 7930 3477 ext 1446 or publications@abpi.org.uk). The publication has been sent to NHS executives and managers as well as organizations such as the Royal Colleges and others. Many health professionals have also been supplied with copies.

Health Select Committee

The Health Select Committee inquiry into the influence of the pharmaceutical industry on health policies, health outcomes and future health priorities and needs continues.

The inquiry covers six main areas: drug innovation; conduct of medical research; provision of drug information and promotion; professional and patient education; regulatory review of drug safety and efficacy and product evaluation.

Many organizations, including the Prescription Medicines Code of Practice Authority, have submitted evidence to the inquiry.

Goodbye Lisa

Lisa Matthews who has been with the Authority for six years as secretary to Etta Logan and Jane Landles will be leaving this month. Lisa has a new job at a firm of architects, interior designers and surveyors in her home town in Kent. The Authority thanks Lisa for her help and wishes her all the best for the future.

Price reductions

As companies are aware, the revised Pharmaceutical Price Regulation Scheme requires prices of medicines to be reduced with effect from 1 January 2005 so as to achieve an overall reduction for a company of 7%.

It is in the interest of advertisers to indicate the new lower prices on promotional material as soon as possible. In the period 1 January to 31 March 2005, however, promotional material will not be considered to be in breach of the Code if it still carries the previous higher price.

Care should be taken, however, to ensure that there is no discrepancy between what representatives say and what is said on written material left with the doctor etc by the representative as this could give rise to complaints.

It will not be acceptable at any time to give comparative prices in promotional material where these involve the new lower price of the advertiser's product and the superseded higher prices of competitor products.

Every effort should be made to ensure that journal advertisements are correct at the time of publication.

Code changes

The European Federation of Pharmaceutical Industries and Associations (EFPIA) has recently reviewed the European Code of Practice for the Promotion of Medicines. Member Associations are required to include the EFPIA Code requirements in their national codes subject to applicable national law. The EFPIA Code was established in 1992 and revised in 1993 to comply with Council Directive 92/28/EEC on the advertising of medicinal products for human use.

The revision of the EFPIA Code is nearly complete. The ABPI and the Authority, as well as many companies, have been involved in the process. The revised EFPIA Code is expected to be agreed shortly.

As part of the review of the EFPIA Code, codes of conduct within the industry across Europe are also being reviewed. The ABPI is in the process of a review of the Code and its operation. Part of that review will include bringing the ABPI Code into line with the new EFPIA Code. Many amendments to the EFPIA Code reflect the current requirements of the ABPI Code. Some will require changes to the ABPI Code.

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 dates on which places remain available are:

Monday, 17 January

Friday, 18 March

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

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

How to contact the Authority

Our address is:

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

www.pmcpa.org.uk

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Jean Rollingson (020 7930 9677 extn 1443).

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/1516/9/03

PFIZER v ALLERGAN

Promotion of Lumigan

Pfizer complained that in the course of promoting Lumigan (bimatoprost eye drops), Allergan was offering an ophthalmic slit lamp or equivalent educational grant to any clinician who started twenty patients on the product. The scheme was known as the Lumigan Case Study Reports initiative. Pfizer alleged that this was an inducement to prescribe. This activity had been brought to Pfizer's attention by several clinicians, therefore bringing discredit to the industry.

The Panel noted that materials for the Lumigan Case Study Reports initiative were provided to ophthalmologists by Allergan representatives. No data collected by the ophthalmologists was provided to Allergan and the company submitted that a payment was made only if requested by the ophthalmologist. The payment, in the form of either a slit lamp costing approximately £175 or an educational grant of £250, was a recompense for the administrative time spent.

The Panel did not consider that the Lumigan Case Study Reports initiative was a *bona fide* clinical study. In intercompany correspondence Allegan had stated that the initiative was not a clinical trial. Allergan stated that the Lumigan Case Study Reports initiative was for ophthalmologists to undertake their own evaluation of Lumigan after it was prescribed in the usual way. The results could be used by the ophthalmologists to support formulary applications, present a summary of data back to the department or for presentations or journal submissions. The representatives' briefing material issued when the initiative was piloted stated that the pilot study would ascertain if the initiative would aid formulary application and be a useful tool for doctors. The Panel considered that whilst ophthalmologists might find the case study report forms helpful, the payment of a fee in the form of either a slit lamp or an educational grant in association with the use of Lumigan amounted to an unacceptable inducement to prescribe the product. In effect the arrangements amounted to paying doctors to prescribe Lumigan. It was irrelevant that the payment was only made upon request from the ophthalmologist.

The Panel ruled a breach of the Code. The Panel considered that the arrangements brought discredit upon and reduced confidence in the pharmaceutical industry and a breach of Clause 2 of the Code was ruled. The Panel was very concerned about the arrangements and reported Allergan to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

At the consideration of the report Allergan stated that it accepted the Panel's rulings and gave details of the steps taken to avoid similar breaches of the Code in the future. Allergan also volunteered for an audit of its procedures.

The Appeal Board was very concerned about the activities; just over 100 ophthalmologists had been supplied with slit lamps or an educational grant. The Appeal Board considered that although the activity had ceased Allergan would have gained a considerable advantage.

The Appeal Board noted Allergan's offer to undergo a voluntary audit, but decided to require the company to undergo a compulsory audit of its procedures relating to the Code as set out in Paragraph 10.4 of the Constitution and Procedure. Upon receipt of the audit report the Appeal Board would consider whether further action was necessary.

The Appeal Board was very concerned that a large number of clinicians might be left with the impression that the arrangements were acceptable and so it required Allergan to take steps to recover the slit lamps and educational grants as set out in Paragraph 10.3 of the Constitution and Procedure. The outcome of the steps to recover the lamps and educational grants would be discussed at the audit.

Upon receipt of the audit report the Appeal Board considered that there were a number of problems in the company. It was of concern that Allergan had not initially known the actual numbers of slit lamps and educational grants distributed. The Appeal Board noted that Allergan accepted the findings of the audit report and acknowledged that there were a number of areas to which it had paid insufficient attention. Allergan would ensure that the report recommendations were acted upon. Nevertheless this was a serious matter. The Appeal Board decided that Allergan should be re-audited within 3 months. It also decided that the case warranted a report to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure. The report to the ABPI Board would be made after the Appeal Board had considered the report on the follow-up audit.

Upon receipt of the report of the follow-up audit the Appeal Board noted that substantial progress had been made on implementing the recommendations of the first audit. Given that it had already decided to report the matter to the ABPI Board, the Appeal Board decided to take no additional action.

The ABPI Board of Management noted Allergan acknowledged that a serious error had been made; the company had undergone two audits and had been required by the Appeal Board to recover the items. The ABPI Board considered that Allergan had demonstrated through the actions taken with its standard operating procedures, communication and training that it was doing everything it could to correct the acknowledged deficiencies. The ABPI Board decided that no further action should be taken.

Pfizer Limited complained about the promotion of Lumigan (bimatoprost eye drops) by Allergan Limited.

COMPLAINT

Pfizer stated that Allergan was currently offering an ophthalmic slit lamp or equivalent educational grant,

to any clinician who started twenty patients on Lumigan. The activity, termed the Lumigan Case Study Reports initiative was acknowledged by Allergan in its letter of 4 September 2003 to Pfizer. A copy of the letter was provided. Allergan had confirmed that representatives were distributing slit lamps following participation in this programme.

Pfizer alleged that this was an inducement to prescribe in breach of Clause 18.1 of the Code. This activity had been brought to Pfizer's attention by several clinicians, therefore bringing discredit to the industry and a breach of Clause 2 of the Code was alleged.

RESPONSE

Allergan stated that Lumigan was launched in the UK in April 2002. Initial feedback from customers showed that the availability of Lumigan was governed by the local hospital formulary which in turn was usually guided by evidence based assessment and by the consultant ophthalmologist's personal view and experience with the product.

Allergan worked with four ophthalmologists to design a tool that would assist other ophthalmologists to gain experience with Lumigan and develop their view of the product.

The case study reports were intended to help ophthalmologists to objectively assess Lumigan in the clinical setting. Summaries of the data collected could be presented back to the department, used as additional and supportive information for a drugs and therapeutics committee application to have the product listed on the formulary, or, in the event of a more refractory case, written up for presentation or journal consideration. The patient evaluation form was designed to collect the most pertinent data but also allowed the ophthalmologist to collect any other additional information considered appropriate. The case studies produced were solely for the use of the hospital and therefore the data collected was for hospital use only.

The data collection form was designed to capture appropriate medical and drug history and demographic information. It allowed for three visits including baseline and offered the option to collect patient feedback. A copy of the pack given to ophthalmologists involved in the initiative was provided.

The Lumigan Case Study Reports initiative started in September 2002. Initially three representatives piloted the scheme. The initiative was rolled out to the rest of the ophthalmology sales team at the end of January 2003 and ran until 30 April 2003. After this date no further packs were supplied to ophthalmologists. The representatives were asked to follow up with those ophthalmologists involved in the initiative until the end of July 2002. In practice, a number of ophthalmologists were still using the Case Study Reports.

The three representatives who piloted the scheme were briefed on this initiative at the sales meeting in September 2002. Subsequently, at the sales meeting in January 2003 a workshop was run for the entire sales team to discuss the wider implementation of this initiative. Copies of the relevant sections of the material presented at both meetings were provided.

The representatives were asked to contact 500 target ophthalmologists regarding this initiative. Overall, 305 ophthalmologists agreed to evaluate Lumigan using the Case Study Reports initiative (102 in the pilot phase and a further 203 between February and April 2003).

In some instances, an ophthalmologist might have spent a significant amount of administrative time preparing a report (or similar) on their observations; as recompense Allergan provided the department with a slit lamp. On a small number of occasions when recompense was requested but the ophthalmologist did not wish to receive a slit lamp an educational grant of £250 was paid to the department. The provision of a slit lamp or an educational grant was only considered when there was a clear request for recompense for time involved in the preparation of a report (or similar) and after such was seen (but not taken away) by the representative. Allergan had supplied 91 ophthalmologists with hand-held ophthalmic slit lamps and 14 with an educational grant. The cost per unit to Allergan for each lamp was approximately £175.

Allergan did not consider that the initiative constituted an inducement to prescribe and did not agree that there was a breach of Clause 18.1 or Clause 2 of the Code.

PANEL RULING

The Panel noted that the Lumigan Case Study Reports initiative had been developed by ophthalmologists working with Allergan. The materials were provided to ophthalmologists by Allergan representatives. No data collected by the ophthalmologists was provided to Allergan and the company submitted that a payment was made only if requested by the ophthalmologist. The payment took the form of either a slit lamp costing approximately £175 or an educational grant of £250. Allergan submitted that the provision of a lamp or the educational grant was a recompense for the administrative time spent.

The Panel noted that Allergan had been asked to supply comprehensive details of the Lumigan Case Study Reports initiative. In the Panel's view the documentation provided by Allergan was limited. With regard to its representatives, no briefing material had been provided, although copies of slides used at two meetings had been supplied. With regard to the ophthalmologists, Allergan had provided a folder which was given to those involved in the initiative; it consisted solely of case report forms and information for patients. There was no written explanation as to the use or purpose of the materials. The case study report form referred to completion of an adverse event form but this had not been provided. The folder included prescribing information. Despite the lack of available detail as to how the Lumigan Case Study Reports initiative was run, the Panel nonetheless considered that sufficient information had been supplied for it to make a ruling.

The Panel did not consider that the Lumigan Case Study Reports initiative was a *bona fide* clinical study. In intercompany correspondence Allegan had stated that the initiative was not a clinical trial. Allergan stated that the Lumigan Case Study Reports initiative was for ophthalmologists to undertake their own evaluation of Lumigan after it was prescribed in the usual way. The results could be used by the ophthalmologists to support formulary applications, present a summary of data back to the department or for presentations or journal submissions. The representatives' briefing material from the September 2002 sales meeting stated that the pilot study would ascertain if the initiative would aid formulary application and be a useful tool for doctors. The Panel considered that whilst ophthalmologists might find the case study report forms helpful, the payment of a fee in the form of either a slit lamp or an educational grant in association with the use of Lumigan amounted to an unacceptable inducement to prescribe the product. In effect the arrangements amounted to paying doctors to prescribe Lumigan. It was irrelevant that the payment was only made upon request from the ophthalmologist.

The Panel ruled a breach of Clause 18.1 of the Code. The Panel considered that the arrangements brought discredit upon and reduced confidence in the pharmaceutical industry and a breach of Clause 2 of the Code was ruled. The Panel was very concerned about the arrangements and decided to report Allergan to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BOARD CONSIDERATION

At the consideration of the report Allergan stated that it accepted the Panel's rulings and had taken a number of steps to avoid similar breaches of the Code in the future. These included updating and revising the standard operating procedure (SOP) for promotional copy and training staff on the revised SOP and the importance of the process. The training emphasised previous areas of weakness; these being a brief as to how items were to be used, documentation for the representatives and documentation for customers (eg clinicians). Allergan volunteered for an audit of its procedures.

As background information Allergan explained that its structure and product portfolio had changed in July 2002. There had been no internal copy approval expertise from April 2002 until mid October 2002. There had been many new recruits and a failure to train new personnel. Outdated processes were in place which were not well designed leading to the approval of the Lumigan Case Study Reports initiative pack without the full context of how it would be used. The arrangements would be in accordance with the Code without the provision of the slit lamps/educational grants. There was a lack of supporting documentation and no full understanding of the context for use of the pack. The full arrangements, including the provision of slit lamps/educational grants, were not approved.

The Appeal Board noted from Allergan that its sales representatives had been informed by voicemail and email that the Lumigan Case Study Reports initiative had ceased and further training would be provided.

The Appeal Board was very concerned about the activities. It noted that 91 ophthalmologists had been supplied with hand-held ophthalmic slit lamps and 14 with an educational grant for £250. The Appeal Board considered that although the activity had ceased Allergan would have gained a considerable advantage.

The Appeal Board noted Allergan's offer to undergo a voluntary audit, but decided that the company should be required to undergo a compulsory audit of its procedures relating to the Code as set out in Paragraph 10.4 of the Constitution and Procedure. Following receipt of the audit report the Appeal Board would then consider whether further action was necessary.

The Appeal Board was very concerned that a large number of clinicians might be left with the impression that the arrangements were acceptable. The Appeal Board decided to require Allergan to take steps to recover the slit lamps and educational grants as set out in Paragraph 10.3 of the Constitution and Procedure. The Appeal Board decided that Allergan should write to each clinician to whom a lamp or educational grant had been supplied to request, where practicable, its return. The outcome of the steps to recover the lamps and educational grants would be discussed at the audit.

FURTHER CONSIDERATION BY THE APPEAL BOARD

Upon receipt of the audit report the Appeal Board considered that there were a number of problems in the company. It was concerned that Allergan had not initially known the actual numbers of slit lamps and educational grants distributed. The Appeal Board noted that Allergan accepted the findings of the audit report and acknowledged that there were a number of areas to which it had paid insufficient attention. Allergan had established a cross functional team to respond to the audit report and ensure that its recommendations were acted upon. Nevertheless this was a serious matter. The Appeal Board decided that Allergan should be re-audited within 3 months. It also decided that the case warranted a report to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure. The report to the ABPI Board would be made after the Appeal Board had considered the report on the follow-up audit.

Upon receipt of the report of the follow-up audit, the Appeal Board noted that substantial progress had been made on implementing the recommendations of the first audit. Given that it had already decided to report the matter to the ABPI Board, the Appeal Board decided to take no additional action.

REPORT TO ABPI BOARD OF MANAGEMENT

Upon receipt of the report from the Appeal Board, the ABPI Board of Management noted Allergan acknowledged that a serious error had been made.

The ABPI Board also noted that Allergan had undergone two audits and had been required by the Appeal Board to recover the items. The ABPI Board considered that Allergan had demonstrated through the actions taken with its standard operating procedures, communication and training that it was doing everything it could to correct the acknowledged deficiencies. The ABPI Board decided no further action should be taken.

Complaint received	**15 September 2003**
Undertaking received	**11 November 2003**
PMCPA proceedings completed	**17 June 2004**
ABPI Board of Management proceedings completed	**14 September 2004**

CASE AUTH/1519/9/03

PRIMARY CARE TRUST CLINICAL GOVERNANCE LEAD v TRINITY

Practice switch programme

The clinical governance lead at a primary care trust (PCT) complained about a Pulvinal salbutamol switch programme undertaken by Trinity.

The complainant stated that concerns were raised when the PCT head of medicines management was contacted by a practice which had had a problem printing a prescription for a patient who had been changed to Pulvinal salbutamol as part of the Pulvinal switch programme. Further investigations revealed that a 'freelance' pharmacist, paid for by Trinity, carried out the switch on 23 July 2003. The PCT understood that the pharmacist carried out the patient searches and made the changes to prescribing on the practice computer system. The company had been asked to supply a copy of the protocol followed in the programme. It had supplied some paperwork and informed the PCT that the spreadsheet [which was headed 'Changing to Pulvinal' and detailed prices of various asthma medicines including, *inter alia*, their unit price, cost per puff and saving with Pulvinal] was the protocol. The PCT did not consider this was an appropriate protocol – it expected to see details of how the change was to be implemented, eg patient recall, patient letters, etc. Trinity had been unable to supply a copy of the confidentiality agreement used. The practice contract was approved and signed on 25 July, although the work was actually carried out at the practice on 23 July.

The Panel noted that Trinity had provided four documents which described four stages of the switch service, known as Concept; search to identify areas of rationalisation; analysis, to allow the health professional to make an informed decision; implementation and review. Each stage was signed off and managed by the project co-ordinator. Reference was also made to a switch co-ordinator whose role was described as non-promotional. The documents referred to the Concept modified release product range and one featured a bar chart comparing Trinity brands with other modified release brands.

The Panel noted the arrangements at the practice in question. A document, provided by the complainant, headed 'Trinity Pharmaceuticals Practice Switch Contract' in which the practice agreed to the switch process did not indicate which products were to be switched, in fact no mention was made of any changes in medication. The document was signed by a GP and dated 25 July. The date booked for the switch was given as 23 July. The complainant had also provided two undated letters signed by Trinity's representative. The letters described the representative as project manager. One was addressed to two GPs of the practice and it was unclear to whom the other was addressed as only the first name had been used. Both letters included details of Pulvinal salbutamol and Pulvinal beclometasone dipropionate (BDP) and neither included prescribing information. Both letters also referred to a Pulvinal inhaler containing formoterol and BDP 'which would be available in the not too distant future'. The complainant also sent a chart headed 'Changing to Pulvinal', which presented a table of data showing the savings that could be made by changing patients from other inhalers/devices to Pulvinal BDP and Pulvinal salbutamol. Beneath the table of data was reference to prescribing information printed overleaf. It appeared that this document might have been sent with the letter to two GPs of the practice.

The Panel noted that the switch at the practice in question had taken place before the relevant form had been signed. The form lacked detail and the Panel thus queried whether the form was sufficient in any event. The representative had used his own letters and not those provided by the company. The Panel noted a letter dated 30 September from the freelance pharmacist who had carried out the switch to Trinity's head office which stated that she was to identify repeat prescriptions for target drugs and devices and 'where appropriate initiate a new repeat master for the equivalent Pulvinal product(s)….'. The Panel considered that potentially changes could have been made to patients' therapy on the practice database by the pharmacist without such changes being authorized by a GP. Trinity submitted that the medication review in question was undertaken exactly in line with the wishes of the GP requesting the review. It accepted that the representative who set up the switch programme had breached company policy and procedures by not having the switch agreement signed and by not using company approved materials. The Panel noted that Trinity had not provided any documentation from the practice in question to show unequivocally what

switches had been agreed. Medication changes had been made without the written agreement of the GP.

The Panel considered that, as implemented in the practice in question, the patient review was in effect linked to the prescription of Trinity's products. A breach of the Code was ruled in this regard.

The Panel considered that the audit arrangements, documentation and training were inadequate. There were no clear, comprehensive instructions about the switch process from the time it was raised by the representatives with practices through to the activities of the pharmacist/nurse. Nor was there documentation setting out all the arrangements for a practice to see before agreeing to the process. The Panel thus considered that the switch process did not meet the supplementary information of the Code in relation to the provision of medical and educational goods and services. The Panel considered that the overall arrangements and documentation were such that the service was inextricably linked to the promotion of Trinity's medicines and amounted to an unacceptable inducement to prescribe. In that regard the Panel noted the freelance pharmacist's letter whereby it appeared that if any change to a patient's repeat prescription was to be made at all it was a change to Pulvinal products. The Panel ruled a breach of the Code in relation to the arrangements for the switch process in general. High standards had not been maintained as acknowledged by Trinity. A breach of the Code was ruled.

The Panel noted that a pharmacist, sponsored by Trinity, had changed patients' prescriptions without prior written agreement from the GP. The Panel considered that such action brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel was very concerned about Trinity's arrangements in general and what had happened at the practice in question and decided to report Trinity to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board was extremely concerned about the overall arrangements for the audit and switch service and decided that Trinity should undergo an audit of its procedures relating to the Code.

Upon receipt of the audit report the Appeal Board was very concerned that patients with stable asthma were being switched to Trinity's products without their knowledge or consent. It was noted that some patients were being switched due to the discontinuation of their current device/medicine. The Appeal Board was also concerned that Trinity had not completely understood that its activities were unacceptable. The amended service was still of serious concern particularly with regard to the failure to separate the service from the promotion of specific medicines.

The Appeal Board was extremely concerned regarding the ethical issues raised by the arrangements. Trinity was, in effect, using sales representatives to advocate switching stable patients to Trinity's medicines. The switch would be carried out by a Trinity employee. In the Appeal Board's view any change in medication might destabilise some patients. The patients who were not switched were those that were too young for Pulvinal, elderly patients, those with complicated or uncontrolled asthma and those who had visited the practice only recently for a prescription. Doctors were not given details of patients who were not switched.

The Appeal Board decided that the matter should be reported to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure. The Appeal Board considered that it would have required Trinity to issue a corrective statement if it had the power to do so. The Appeal Board therefore recommended that the ABPI Board consider such an option. The Appeal Board also decided that Trinity should be re-audited within 3 months and that it must take immediate action to separate the roles of the project co-ordinator and the clinical support specialist.

The Appeal Board was deeply concerned about the findings of the follow-up audit and the lack of progress made since the first audit. However given that the matter had been reported to the ABPI Board, the Appeal Board decided to take no further action.

The ABPI Board of Management noted the actions taken by Trinity to implement the recommendations of both audits. The ABPI Board had some concerns about the arrangements but decided that as some corrective steps had been taken no further action was necessary at this stage. It should be emphasised to Trinity that rigorous procedures must be employed and adhered to. The ABPI Board reserved the right to require a further audit.

The clinical governance lead at a primary care trust (PCT) complained about a Pulvinal switch programme undertaken by Trinity Pharmaceuticals Limited.

COMPLAINT

The complainant stated that concerns were raised when the PCT head of medicines management was contacted by a practice which had had a problem printing a prescription for a patient who had been changed to Pulvinal salbutamol as part of the Pulvinal switch programme. Further investigations and discussions with the company and practice revealed that a 'freelance' pharmacist, paid for by Trinity, carried out the switch on the practice computer on 23 July 2003. The PCT understood that the pharmacist carried out the patient searches and made the changes to prescribing on the practice computer system. The company had been asked to supply a copy of the protocol followed in the programme. It had supplied some paperwork (copies were supplied) and informed the PCT that the spreadsheet [which was headed 'Changing to Pulvinal' and detailed prices of various asthma medicines including, *inter alia*, their unit price, cost per puff and saving with Pulvinal] was the protocol. The PCT did not consider this to be an appropriate protocol – it expected to see details of how the

change was to be implemented, eg patient recall, patient letters, etc. The company had been unable to supply a copy of the confidentiality agreement used. The practice contract was approved and signed on 25 July 2003, although the work was actually carried out at the practice on 23 July 2003.

When writing to Trinity the Authority asked it to respond in relation to Clauses 2, 9.1 and 18.1 of the 2003 edition of the Code.

RESPONSE

Trinity stated that it manufactured and distributed off-patent medicines, using novel delivery systems and presentations which cost substantially less than the originator products and provided value for money. Customers saw this as an important benefit in the current environment and continued heavy downward pressure on drugs budgets. Trinity offered a medication review and switch service to GPs in which a Trinity-sponsored pharmacist reviewed a particular area of prescribing where rationalisation could provide a cost saving. One of the areas of interest, and an area of concern to many cost-conscious prescribers, was the use of dry-powder inhalers for asthma.

Trinity confirmed that this type of medication review was conducted at the surgery in question on 23 July. This review was undertaken by an experienced independent pharmacist, whom Trinity understood to be familiar to the PCT in question. [The complainant stated that the independent pharmacist was not familiar to the PCT.] The work was done in line with the wishes of the GP who had requested the review; Trinity was unaware of any concerns about this work from any member of staff at this practice.

The company's standard practice, and the one on which its representatives were trained, was that the requesting GP should sign a practice switch contract before the work was undertaken. The parameters on which the pharmacist carried out the search and identified patients was a matter for the pharmacist and doctor to agree. The completed list of identified patients was then reviewed by the doctor to agree, prior to the changes being made. The precise details of how patients would be told of the changes varied according to practice requirements. The pharmacist was able to facilitate this process if required, but the communication between the practice and the patients must remain correspondence between those two parties. Representatives were not involved at any stage in the switch process.

Whilst there was no obligation to enter into written agreements with clinicians, Trinity believed it good practice to sign a confidentiality agreement before any work started. Unfortunately it appeared that the representative who set up the switch programme in this practice breached two aspects of company policy and procedure. Firstly, that a switch agreement form should be signed before any work was undertaken and secondly that all materials provided to customers must first be internally approved. Trinity regarded these breaches as extremely serious and had instigated disciplinary procedures against the representative in question.

Trinity regretted that its provision of the service to this practice had created concern for the complainant and it submitted that its services and procedures, when carried out as defined, were consistent with the Code.

Trinity did not accept that any aspect of its service constituted a breach of Clause 18.1. The service was offered to GPs as a non-promotional medication review. The pharmacist and doctor agreed which medications should be reviewed and changed. The doctor agreed any medication changes that were to be made: there was no requirement for any switches, or indeed any particular product to be used. Representatives were not involved in the switch process at any point. Trinity strongly resisted any suggestion that this service constituted inducement to prescribe.

In this case though, Trinity acknowledged that its representative did not maintain the company's required standards and therefore admitted a breach of Clause 9.1. However, the practice staff had no complaints about the representative or the service received. Whilst Trinity regarded the representative's breach of company procedures and failure to maintain high standards to be extremely serious, it did not consider that the representative's activities brought discredit on the industry or merited particular censure. It therefore denied any breach of Clause 2.

In response to a request for additional information Trinity stated that the switch programme was a service provided at the request of a practice in which patients' medication was reviewed with the aim of reducing prescribing costs while maintaining clinical outcomes. The switch service was entirely non-promotional and was not linked to the use of any particular product – in fact, it was the Practice (not Pulvinal) Switch Programme. The representative had no involvement with the switch process or patient data. The representative only conducted the initial audit using anonymous patient identification numbers, such that the practice was provided with a cost-savings report indicating the savings that 'could' be made. Representatives did not access patient records that could identify individual patients. Practices were then provided with the services of either a qualified nurse or pharmacist to review the practice-prescribing database and suggest appropriate changes. Switches and subsequent communication with patients were agreed between the practice and the nurse/pharmacist. A letter from the pharmacist, who conducted the review at the practice in question, which outlined the process, was provided together with an example of a patient letter.

As noted above the sales representative, acting as the project co-ordinator for this practice switch programme, did not follow company procedures and was now subject to a disciplinary process. All members of the sales force had been reminded about the need to adhere to company procedures relating to approval of items to be used with customers and conduct of practice switch programmes.

In response to a further request for more information Trinity stated that the instruction issued to representatives in the audit process comprised training on the initial training course and subsequently 'hands on' training in the field.

A similar system existed for training the in-house switch co-ordinators, the difference being that switch co-ordinators required more in-depth understanding of the systems themselves to allow the individual identification of patients and subsequent changes to their medication. The correspondence from the freelance pharmacist employed to carry out the practice switch had been provided.

Trinity reiterated that the letters written by the representative were not approved. The representative should have submitted draft correspondence to head office for approval. Each initial training course included a presentation on the Code and outlined the need for compliance and the procedures required for submitting materials for approval.

The 'Dear Patient' letter headed 'Asthma Inhaler Review' on surgery headed notepaper was not based on a template provided by the company. Part of the role of the freelance pharmacist was to encourage the practice to develop its own materials for communicating with patients whose treatment had changed.

Trinity provided four documents. These being a document 'Putting you in a winning position' (TR491-April 2002) which referred to Trinity MR brands and included a cost comparison of the most expensive modified release brands and Trinity MR brands. This document appeared to be for the prescriber. Another document 'Concept' 'Putting you in a winning position' (TR502-April 2002) described Trinity's 'innovative prescribing support service' Concept. Another document (TR490-April 2002) referred to Concept as a 'simple solution to rational prescribing'. The fourth document (TR704-June 2003) described the Concept service and the Trinity Pharmaceuticals Switch Co-ordinator (Pharmacist) and appeared to be designed to give to practices once they had decided to implement Concept.

PANEL RULING

The Panel noted that Trinity had provided four documents which described four stages of the switch service, known as Concept; search to identify areas of rationalisation; analysis, to allow the health professional to make an informed decision; implementation and review. Each stage of the process was signed off and managed by the project co-ordinator. Reference was also made to a switch co-ordinator whose role was described as non-promotional. The documents referred to the Concept modified release product range and one featured a bar chart comparing Trinity brands with other modified release brands.

The Panel noted the arrangements at the practice in question. A document, provided by the complainant, headed 'Trinity Pharmaceuticals Practice Switch Contract' (TR369) in which the practice agreed to the switch process did not indicate which products were to be switched, in fact no mention was made of any changes in medication. The document was signed by a doctor in the practice and dated 25 July 2003. The date booked for the switch was given as 23 July 2003. The complainant had also provided two undated letters signed by the Trinity representative who was described as Project Manager. One was addressed to two doctors in the practice and it was not clear to whom the other was addressed as only the first name had been used. Both letters included details of Pulvinal salbutamol and Pulvinal beclometasone dipropionate (BDP) and neither referred to or included prescribing information. Both letters also referred to a Pulvinal inhaler containing formoterol and BDP 'which would be available in the not too distant future'. The complainant also sent a chart headed 'Changing to Pulvinal' (ref TR447), which presented a table of data showing the savings that could be made by changing patients from other inhalers/devices to Pulvinal BDP and Pulvinal salbutamol. Beneath the table of data was reference to prescribing information printed overleaf. It appeared that this document might have been sent with the letter to the two doctors in the practice.

The Panel considered that Trinity's response was confusing and lacked detail, particularly with regard to the training of staff and the existence of documents in relation to the switch process. The Panel considered nonetheless that sufficient information had been supplied for it to make a ruling.

The Panel noted that the switch at the practice in question had taken place before the relevant form had been signed. The form lacked detail and the Panel thus queried whether the form was sufficient in any event. The representative had used his own letters and not those provided by the company. The Panel noted a letter from the freelance pharmacist dated 30 September to Trinity's head office which stated that she was to identify repeat prescriptions for target drugs and devices and 'where appropriate initiate a new repeat master for the equivalent Pulvinal product(s)….'. The Panel considered that potentially changes could have been made to patients' therapy on the practice database by the pharmacist without such changes being authorized by a GP. Trinity submitted that the medication review in question was undertaken exactly in line with the wishes of the GP requesting the review. It accepted that the representative who set up the switch programme had breached company policy and procedures in two aspects. Firstly by not having the switch agreement signed and secondly by not using company approved materials. The Panel noted that Trinity had not provided any documentation from the practice in question to show unequivocally what switches had been agreed. Medication changes had been made without the written agreement of the GP.

The Panel considered that, as implemented in the practice in question, the patient review was in effect linked to the prescription of Trinity's products. A breach of Clause 18.1 was ruled in this regard.

The Panel considered that the audit arrangements, documentation and training were inadequate. There were no clear, comprehensive instructions about the switch process from the time it was raised by the representatives with practices through to the activities of the pharmacist/nurse or documentation setting out all the arrangements for a practice to see before agreeing to the process. It thus considered that the switch process did not meet the supplementary information to Clause 18.1 of the Code in relation to the provision of medical and educational goods and

services. The Panel considered that the overall arrangements and documentation were such that the service was inextricably linked to the promotion of Trinity's medicines and amounted to an unacceptable inducement to prescribe. In that regard the Panel noted the freelance pharmacist's letter whereby it appeared that if any change to a patient's repeat prescription was to be made at all it was a change to Pulvinal products. The Panel ruled a breach of Clause 18.1 in relation to the arrangements for the switch process in general. The Panel considered that high standards had not been maintained as acknowledged by Trinity. A breach of Clause 9.1 was ruled.

With regard to Clause 2, the Panel noted that a ruling of a breach of that clause was a sign of particular censure and reserved for such use. The matter in hand involved an audit pharmacist, sponsored by Trinity, who had changed patients' prescriptions without prior written agreement from the doctor. The Panel considered that such action brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

During its consideration of this case the Panel considered that the letter to the practice from the representative was promotional and should have included prescribing information and been certified. It also appeared to promote an unlicensed medicine, the combination inhaler, formoterol and BDP. The representative had signed the letter as project manager; it was thus not clear that he was a representative. The Panel was also concerned that part of the role of the freelance pharmacist was to encourage the practice to develop its own materials for communicating with patients whose treatment had changed. The Panel did not know the precise process for generating such material but was concerned that the system could be used to circumvent the need to have documents approved for use under the Code. The patient letter provided by the freelance pharmacist contained a number of claims for the Pulvinal inhaler. The document (TR491-April 2002) provided by Trinity which set out the Concept process referred to specific Trinity modified release (MR) brands and should have included prescribing information for each one as required by Clause 4.1 of the Code. The Panel requested that its concerns be drawn to Trinity's attention.

The Panel was very concerned about Trinity's arrangements in general and what had happened at the practice in question and decided to report Trinity to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BOARD CONSIDERATION

The Appeal Board was extremely concerned about the overall arrangements for the audit and switch service. The Appeal Board decided that, as set out in Paragraph 10.4 of the Constitution and Procedure, Trinity should be required to undergo an audit of its procedures relating to the Code. Following receipt of the audit report the Appeal Board would then consider whether further action was necessary.

FURTHER CONSIDERATION BY THE APPEAL BOARD

Upon receipt of the audit report, the Appeal Board was very concerned that patients with stable asthma were being switched to Trinity's products without their knowledge or consent. It was noted that some patients were being switched due to the discontinuation of their current device/medicine. The Appeal Board was also concerned that Trinity had not completely understood that its activities were unacceptable. The amended service was still of serious concern, particularly the failure to separate the service from the promotion of specific medicines.

The Appeal Board was extremely concerned regarding the ethical issues raised by the arrangements. Trinity was, in effect, using sales representatives to advocate switching patients to Trinity's medicines. The switch would be carried out by a Trinity employee who would switch stable patients to Trinity's medication. In the Appeal Board's view any change in medication might destabilise some patients. The patients who were not switched were those that were too young for Pulvinal, elderly patients, those with complicated or uncontrolled asthma and those who had visited the practice only recently for a prescription. Doctors were not given details of patients who were not switched.

The Appeal Board decided that the matter should be reported to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure. The Appeal Board considered that it would have required Trinity to issue a corrective statement if it had the power to do so. The Appeal Board therefore recommended that the ABPI Board consider such an option.

The Appeal Board also decided that Trinity should be re-audited within 3 months and that it must take immediate action to separate the roles of the project co-ordinator and the clinical support specialist.

The Appeal Board was deeply concerned about the findings of the follow up audit and the lack of progress made since the first audit. However given that the matter had been reported to the ABPI Board, the Appeal Board decided to take no further action.

REPORT TO ABPI BOARD OF MANAGEMENT

The ABPI Board of Management noted the actions taken by Trinity to implement the recommendations of both audits. The ABPI Board had some concerns about the arrangements but decided that as some corrective steps had been taken no further action was necessary at this stage. It should be emphasised to Trinity that rigorous procedures must be employed and adhered to. The ABPI Board reserved the right to require a further audit.

Complaint received	**23 September 2003**
Undertaking received	**23 December 2003**
PMCPA proceedings completed	**17 June 2004**
ABPI Board consideration	**14 September 2004**

LILLY v BRISTOL-MYERS SQUIBB and OTSUKA

Promotion of Abilify

Lilly complained that Bristol-Myers Squibb and Otsuka were promoting Abilify (aripiprazole) prior to the grant of a marketing authorization.

The leavepiece 'Achieving a Balance' described the receptor binding of full agonists, antagonists, and partial agonists. The cited reference, Tamminga (2002), dealt with partial dopamine antagonists in the treatment of psychosis and mentioned aripiprazole and stated that it would be marketed by Bristol-Myers Squibb and Otsuka. Lilly stated that since the joint marketing arrangement between the two companies was mainly to commercialise aripiprazole and the joint venture had no other currently marketed products relevant to the messages in the leavepiece, it was difficult to see how the leavepiece, describing known properties of aripiprazole (which was the first antipsychotic recognised to be a partial agonist at the time of its launch anywhere in the world) could be used other than to prompt or solicit a request for information about aripiprazole. Lilly also alleged that the leavepiece was disguised promotion.

The Panel noted that Abilify was not licensed in the UK. It appeared that Bristol-Myers Squibb and Otsuka were using medical representatives to provide information to health professionals ahead of launch.

In considering the allegations regarding the two leavepieces 'Achieving a Balance' and 'Achieving Stability' (below) the Panel also bore in mind the allegation and response in relation to representatives' training (below), as the use of the leavepieces as well as content were relevant factors. The leavepieces were used by medical representatives as part of introductory discussions about ligand-receptor interactions.

The Panel noted that the leavepiece, 'Achieving a Balance' did not mention a product by either brand name or generic name. It featured the receptor binding of agonists, antagonists, and partial agonists and was referenced to Tamminga (2002) which discussed partial dopamine agonists in the treatment of psychosis and referred to aripiprazole. The back page gave details of useful contacts; three of the four contacts stated were mental health charities, two of which were linked particularly with schizophrenia. In the Panel's view the cited reference and the list of contact details gave an implied reference to an antipsychotic medicine.

The Panel considered that overall the features the representatives were to discuss with health professionals were closely associated with Abilify. The Panel considered that such activity did not constitute the legitimate exchange of medical or scientific information during the development of a product and went beyond the provision of corporate information about an area of research. The leavepiece formed an integral part of the information provided by representatives, which when considered in its totality was, in the Panel's view, associated with Abilify which did not have a marketing authorization. The leavepiece and its provision by the representatives in this context amounted to a breach of the Code and the Panel ruled accordingly. The Panel did not consider that the leavepiece was disguised; it would not be seen as anything other than a promotional item. The Panel thus ruled no breach of the Code.

The leavepiece 'Achieving Stability' consisted of four pages and discussed the activities of agonists, antagonists and partial agonists in relation to the hypoactive and hyperactive system.

Lilly stated the inside double-page spread showed graphs indicating how full agonists, antagonists and partial agonists might act in the setting of a hypoactive system and a hyperactive system. The back page stated, beneath a heading 'Stabilising Activity', that agonists were effective in a hypoactive system, antagonists were effective in a hyperactive system and that partial agonists had the overall ability to reduce activity in a hyperactive system and to increase activity in a hypoactive system. The statements were referenced to Stahl (2001) which described the mode of action of aripiprazole. Lilly made similar allegations to those made about the 'Achieving a Balance' leavepiece.

The Panel noted its general comments above. The 'Achieving Stability' leavepiece was to be used by representatives for three months following the use of the leavepiece 'Achieving a Balance' at issue above. The Panel noted that the leavepiece 'Achieving Stability' did not mention a product by either brand name or generic name. The leavepiece compared the action of agonists, antagonists and partial agonists and was referenced to Stahl which was entitled 'Dopamine System Stabilizers, Aripiprazole and the Next Generation of Antipsychotics'. No details of useful contacts were given. The Panel considered that the leavepiece 'Achieving Stability' and its provision by representatives within the context above amounted to the promotion of Abilify prior to the grant of the marketing authorization. A breach of the Code was ruled. The Panel did not consider that the leavepiece was disguised and thus ruled no breach of the Code in that regard.

Lilly believed the two leavepieces were being used as detailing materials. Lilly considered that it would be difficult for representatives to maintain credibility when talking to psychiatrists about the matters described in the two leavepieces if they had not been trained or otherwise informed about the pharmacological properties of aripiprazole. Clearly training representatives about aripiprazole would not be necessary prior to the grant of a marketing authorization if those representatives were not being encouraged to promote the medicine. Lilly alleged that Bristol-Myers Squibb and/or Otsuka had also breached the Code by encouraging an action which would be in breach of the Code.

The Panel noted that the representatives had received four training modules as part of the 'Arpiprazole Learning System'. The modules did not feature on aripiprazole in detail but references were made to the product including benefits

compared to atypical antipsychotics currently on the UK market. Other training material consisted of four slide presentations, 'Partial Agonism', 'The Competition', 'CNS Business Unit Meeting Cycle 2' dated May 2003 and 'CNS National Conference Bahamas' dated September 2003.

The two CNS business unit presentations were made up of a number of slides each bearing what appeared to be the Abilify product logo. Each presentation referred to the ROAR programme (Receptor Occupancy and Activity Revision). The presentation dated May 2003 included a slide headed 'Critical Success Factors' which instructed representatives to 'Consistently differentiate Abilify as "next generation atypical" emphasising efficacy at every opportunity', 'Drive awareness and enthusiasm across the customer base to ensure rapid uptake at launch' and 'Build relationships with customers of influence to ensure product endorsement'. The subsequent presentation dated September reviewed the ROAR programme and listed the messages psychiatrists had heard associated with Abilify as 'Next generation atypical, superior tolerability and safety, unique mode of action, robust efficacy, partial agonism'. One slide referred to psychiatrists' sources of information on Abilify/aripiprazole followed by a bar chart which listed sales representatives as 49% and convention/conference as 26% (July 2003 data). Another slide stated that the ROAR II Rationale objectives included 'partial agonism MUST be perceived as a basis for unrivalled efficacy'.

The slide presentation 'The Competition' gave details about the strengths and weaknesses of different treatments including Lilly's product Zyprexa. A section headed 'unmet needs' referred to the high risk of weight gain, sedation, dyslipidaemia and diabetes. One slide stated that physicians needed medicines which did not raise concerns about obesity, diabetes and elevated lipids or cardiovascular problems among other things. Another slide stated that patients needed medicines that did not interfere *inter alia* with body weight, alertness and energy.

The slide set 'Partial Agonism' did not mention Abilify. It explained how partial agonism worked in relation to neurotransmitters and referred to partial agonism as a potential solution to complex diseases where neurotransmitter levels might simultaneously be too high in one area of the brain and too low in another area.

The Panel considered that the four slide presentations would encourage the representatives to promote Abilify to health professionals. Psychiatrists' sources of information on Abilify listed representatives as 49% (July 2003), an increase of 13% from March 2003. The role of a medical representative would be seen by the health professionals as promotional. The representatives were encouraged to discuss what, on the launch of Abilify, would be competitor products. Criticising competitor products was a promotional activity.

The Panel did not accept Bristol-Myers Squibb and Otsuka's submission that the representatives had not been trained on Abilify. Further the Panel queried whether any medical representative would receive a genuine unsolicited question about aripiprazole given their role, their training and the materials to be used by them.

None of the materials placed the activities in context. The Panel considered that the representatives' training material would lead to the promotion of an unlicensed medicine. The Panel therefore ruled the briefing material in breach of the Code.

Lilly stated that a medical information request form (that specified aripiprazole) had included the name, territory number, and contact details of a representative of Bristol-Myers Squibb. Lilly was unclear as to why some of these details needed to be included on the form. Lilly again alleged that Bristol-Myers Squibb and/or Otsuka had also breached the Code by encouraging an action which would be in breach of the Code.

With regard to the medical information request form the Panel did not consider that including the representative's details on the form was itself a breach of the Code as alleged and ruled accordingly.

Lilly noted that a Receptor Occupancy and Activation Review (ROAR) lecture was held in Leeds in October 2003 for which arrangements appeared to have been made by a public relations (PR) agency. A similar meeting was held in Wales in October 2003, also organised by a PR agency. The invitation for the Leeds meeting included a reply paid card that would be mailed back to the agency involved. Notably the invitation also contained the name of a representative who was to be contacted for more information.

According to the invitations the talks focused on the receptor pharmacology of atypical antipsychotics; it seemed likely that aripiprazole would be mentioned thus, given the novelty of the concept, promoting discussion about it. The companies therefore appeared to have used their PR agency (with the aid of a company representative) to invite doctors to a lecture touching on an unlicensed product for the purposes of soliciting a discussion about it.

The Panel noted that the invitation stated that the lecture would focus on the important role that receptor pharmacology played in the battle to effectively treat serious mental illness. The lecturer would examine what made an atypical antipsychotic atypical and would review the clinical implications.

The Panel noted that one of the objectives for the peer-to-peer regional meetings in the representatives' briefing material was to 'Continue the positive cascade of anticipation for Abilify'. The Panel also noted that the stand and material available were similar to those at issue above.

The Panel considered that the meetings organised by Bristol-Myers Squibb and Otsuka amounted to a marketing exercise designed to raise awareness of aripiprazole and to raise expectations that the new product might meet some of what were seen as problems with currently licensed medicines. The Panel considered that the ROAR lectures constituted promotion of Abilify prior to the grant of its

marketing authorization and thus ruled a breach of the Code.

Lilly stated that Bristol-Myers Squibb and Otsuka had a stand at a meeting in June – July with exhibition panels carrying the clear statement 'The Road to the Future of Atypicals'. The stand was manned by medical representatives and at least two leavepieces were given out with the same colour scheme/background as the stand livery or branding. The contents of the leavepieces made it clear that the medicine, which would be the future atypical, was aripiprazole.

The Panel noted its comments and rulings upon the provision of the leavepieces, the ROAR programme, the role of representatives and their training above. The Panel noted that the exhibition panels clearly related to a future atypical antipsychotic which would be available from Bristol-Myers Squibb and Otsuka. The Panel considered that the companies' activities went beyond the exchange of medical and scientific information during the development of a medicine. The Panel considered that the exhibition panels amounted to the promotion of Abilify prior to the grant of its marketing authorization; a breach of the Code was ruled. The Panel did not consider that the exhibition panels were disguised; they would not be seen as anything other than promotional. The Panel thus ruled no breach of the Code in that regard.

Lilly also referred to a meeting which had taken place in Manchester. The company further stated that it had received anecdotal reports that a claim was being made that the risk of diabetes with Zyprexa was significantly different from that with aripiprazole despite the fact that data showed this not to be so. Lilly stated that these further instances of disguised promotional meetings and detailing of aripiprazole supported its view that aripiprazole was being promoted prior to the grant of a marketing authorization.

The Panel noted that although the specific meeting in Manchester referred to by Lilly had not, according to Bristol-Myers Squibb and Otsuka, taken place, a meeting which was part of the ROAR programme had. The Panel considered that this meeting was covered by its rulings above. The Panel also considered that the general allegation about the promotion of aripiprazole prior to the grant of a marketing authorization was covered by its previous rulings. With regard to the allegations of what was said in relation to Zyprexa and diabetes the Panel was unable to make a ruling as no clauses had been cited. However it noted its previous comments made in relation to a similar allegation where no *prima facie* case to answer had been ruled. These being that it was concerned that the representatives briefing material did not comply with the Code as it did not reflect the information in the Zyprexa summary of product characteristics (SPC) and the Panel had requested that Bristol-Myers Squibb and Otsuka be advised of its views.

Lilly stated that it had been told by a nurse in Manchester that he had been invited to a local advisory board meeting that took place in the autumn of 2003. Around 50 people were present for the purpose of giving advice and comment on proposed aripiprazole marketing materials. Materials were handed out and then collected at the end of the meeting. The nurse recalled that this meeting was one of a series of maybe four similar such meetings. Payment was made to the attendees. Lilly alleged that this was another example of representatives promoting Abilify prior to the grant of its marketing authorization.

The Panel noted that there was a difference between Lilly's description of the advisory board meeting and that of Bristol-Myers Squibb and Otsuka.

Bristol-Myers Squibb and Otsuka stated that 10 advisory boards had been run with a maximum of 12 persons per advisory board. The invitation to the meeting in July 2003 stated that the companies were convening the advisory board to seek counsel on the current issues surrounding the UK antipsychotic market and to evaluate the aripiprazole data from a UK perspective. Input on the launch of the product to both primary and secondary care would be sought. The invitation also stated that as a follow up the companies anticipated working with some individual members beyond the advisory board meetings. The meetings started at 3.30pm and closed at 7pm followed by dinner. There were three presentations; 'mental health environment', 'mechanism of action and efficacy' and 'tolerability'. There were also workshop breakouts and coffee for 45 minutes and discussion of patient types for 45 minutes. It appeared from the agenda that some sessions would be run by medical personnel and others by marketing.

Bristol-Myers Squibb and Otsuka provided the slides for two presentations, 'Aripiprazole Next Generation Atypical Antipsychotics' and 'Aripiprazole Advisory Panel Meeting'. The slides were branded with what appeared to be the Abilify logo. The 'Aripiprazole Next Generation…' presentation focussed on its 'unique partial agonist mode of action', 'excellent long-term efficacy', stated that it was 'very well tolerated,' and gave results from a study in the US and its use in the US. The final slide listed three topics for discussion; whether the data linked the mode of action of aripiprazole with its efficacy and tolerability profile, what gaps should be addressed, and based on the product's profile asked what the main opportunities were.

The objectives for the 'Aripiprazole Advisory Panel Meeting' presentation were to: 'Validate market research findings, particularly in the area of customer insight and motivation to prescribe; use real-life experiences to understand degree and comfort of using a new anti-psychotic; understand whether aripiprazole is perceived as the latest atypical or the first in a new class and test the sufficiency of the aripiprazole data set'.

The Panel considered that the slides were promotional as they included very strong claims for the product. It did not appear that the companies were asking for views on how the product should be promoted.

The Panel noted the companies' submission that the purpose of the meeting was to understand the

regional mental health environment and to get feedback from key national and regional psychiatrists on the current treatment and management of schizophrenia. The invitation also referred to the evaluation of aripiprazole data from a UK perspective.

The Panel considered that although the invitation mentioned the interactive nature of the meeting, it was not sufficiently clear about the precise role of the invitees in that no mention was made of the £500 payment per attendee. The agenda did not allow much time for feedback from the participants. No pre-reading/work was required. Paying each attendee £500 seemed high for the amount of work done. The Panel queried whether there was sufficient justification for the number of meetings held. The Panel questioned whether all the delegates would have truly acted as consultants, each giving such advice as to justify a £500 honorarium. The Panel considered that it was untenable to argue that the delegates were being employed for their views when the delegates were only informed about payment after the meeting.

The Panel was concerned about the wording of the invitation, the number of meetings held, the materials presented at the meeting and that it was not clear what was expected from the participants. The Panel considered that the arrangements for the advisory board meetings were unacceptable, they constituted a series of promotional meetings for Abilify which was not licensed in the UK. The Panel ruled a breach of the Code.

The Panel noted Bristol-Myers Squibb and Otsuka's submission that representatives had not attended the advisory board meetings. The Panel considered that on the evidence before it the representatives had not promoted Abilify at the advisory board meetings and thus ruled no breach of the Code.

Lilly alleged that Bristol-Myers Squibb and/or Otsuka had failed to maintain high standards. Further the companies had brought the industry into disrepute in breach of Clause 2.

The Panel noted its rulings and considered that neither Bristol-Myers Squibb nor Otsuka had maintained high standards and thus each was ruled in breach of the Code. It also considered that Bristol-Myers Squibb and Otsuka's activities brought discredit upon and reduced confidence in the pharmaceutical industry. Each company was ruled in breach of Clause 2 of the Code.

The Panel was concerned about the nature and scale of the activities and thus reported Bristol-Myers Squibb and Otsuka to the Appeal Board in accordance with the Constitution and Procedure.

During the consideration of the report the Appeal Board noted that the applications for Abilify licenses in the US and in Europe were submitted at about the same time. The US licence was granted in November 2002 following FDA accelerated approval. European approval was anticipated in December 2002 but the Committee for Proprietary Medicinal Products (CPMP) asked for additional information on a number of occasions. The marketing authorization was not issued until June 2004.

The Appeal Board noted that the delayed marketing authorization for Abilify meant that representatives had had to sell other products which were licensed; they had also worked as 'information gatherers' using the two leavepieces 'Achieving a Balance' and 'Achieving Stability'. The companies had accepted that their actions had amounted to the promotion of Abilify prior to the grant of its marketing authorization. The Appeal Board decided that in accordance with Paragraph 10.4 of the Constitution and Procedure, Bristol-Myers Squibb and Otsuka should each be required to undergo audits of their procedures relating to the Code of Practice.

Upon consideration of the audit reports the Appeal Board noted that progress had been made which must continue. These cases concerned a serious matter. Taking all the circumstances into account it decided that the companies should be re-audited in six months' time (March 2005).

Eli Lilly and Company Limited complained about activities of Bristol-Myers Squibb Pharmaceuticals Limited and Otsuka Pharmaceuticals (UK) Ltd with regard to Abilify (aripiprazole).

Abilify was not yet licensed in the UK. It was anticipated that the product would be used to treat schizophrenia. The product was available in the US.

Lilly was concerned that a number of activities constituted promotion prior to the grant of a marketing authorization.

Bristol-Myers Squibb and Otsuka submitted a joint response to the complaint. The companies submitted that their activities in this area to date revolved around building relationships founded on Bristol-Myers Squibb's heritage in psychiatry. Scientific information on the disease area was provided by the medical department upon request.

The companies submitted that the complaints were unfounded and that they had acted at all times in accordance with the Code and in particular those parts of the Code that related to activities permitted prior to the grant of a marketing authorization.

A Detail materials and representative training

1 Leavepiece 'Achieving a Balance'

The leavepiece (ref ABI/04-03/0127/03-05), consisted of four pages. The inside double-page spread which was entitled 'Receptor Binding', and referenced to Tamminga (2002), described the receptor binding of full agonists, antagonists, and partial agonists.

COMPLAINT

Lilly noted that the pages entitled 'Receptor Binding' described the mode of action of full agonists, antagonists and partial agonists. The cited reference, Tamminga, dealt with partial dopamine antagonists in the treatment of psychosis and contained two paragraphs which mentioned aripiprazole and stated that it would be marketed by Bristol-Myers Squibb and Otsuka. Since a major activity of the joint marketing arrangement between the two companies was to commercialise aripiprazole, and since the joint

venture had no other currently marketed products relevant to the messages in the leavepiece, it was difficult to see how the leavepiece, issued in the names of both companies and describing known properties of aripiprazole (which was the first antipsychotic recognised to be a partial agonist at the time of its launch anywhere in the world) could be used other than to prompt or solicit a request for information about aripiprazole. Lilly alleged that the leavepiece was disguised promotion of aripiprazole in breach of Clause 10.1 of the Code and was designed to promote a medicine prior to the grant of a marketing authorization in breach of Clause 3.1.

RESPONSE

Bristol-Myers Squibb and Otsuka stated that the leavepiece was withdrawn from use several months ago. The leavepiece mentioned ligand-receptor interactions and partial agonism and carried the logos of Bristol-Myers Squibb and Otsuka. The purpose was to educate the reader as to the various activation states of receptors. There was no mention of aripiprazole. It therefore could not be seen as promotional so did not breach Clause 10.1 of the Code. As this piece was non-promotional there could be no ruling of a breach of Clause 3.1 of the Code for promoting before the grant of a marketing authorization.

Bristol-Myers Squibb and Otsuka stated that this exchange of background scientific information did not constitute promotion of an individual medicine, nor disguised promotion. The companies disputed that health professionals would necessarily infer the identity of a product from the fact that the two companies were collaborating on this educational programme. Reference to a scientific paper which a reader would have to go to a library or database to look up, and read thoroughly in order to identify one specific medicine amongst a number of other medicines discussed, did not amount to promotion.

In light of the above the companies submitted that there was no breach of either Clause 10.1 or 3.1 of the Code.

In response to a request for further information Bristol-Myers Squibb and Otsuka stated that the two leavepieces 'Achieving a Balance' and 'Achieving Stability' (point A2) were used during introductory discussions with health professionals. The role of the representatives was to introduce themselves, the companies and their heritage in this therapeutic area; to gain information on the local mental healthcare environment; to establish relationships and finally to have introductory discussions focusing on ligand-receptor interactions. The leavepieces depicted general interactions only and were not compound or product specific.

The leavepiece 'Achieving a Balance' was used from May 2003 to September 2003. The leavepiece 'Achieving Stability' was used from September 2003 to November 2003. The only other leavepiece used during this period entitled 'On Track for the Future' (ref ABI/11-02/0076/1004) was provided. The activities of Bristol-Myers Squibb and Otsuka revolved around building relationships founded on their heritage in the area of mental health; the 'On Track for the Future' corporate leavepiece served as a tool for this. Where appropriate the 'Achieving Stability' or 'Achieving a Balance' leavepieces might have been used in addition to the general introduction of the Bristol-Myers Squibb/Otsuka partnership.

With regard to exchanges of background scientific information the companies confirmed that these discussions were limited to general ligand-receptor interactions only. No representative had been involved in exchanging information on aripiprazole in advance of the marketing authorization. Indeed they had had no training on aripiprazole.

A briefing slide headed 'Partial Agonism' was used by the companies' medical advisor to brief medical representatives on partial agonism. The information was very general information on ligand-receptor interactions. The slides pertained to the leavepiece 'Achieving a Balance'. There was no specific brief for 'Achieving Stability', as the principles conveyed by the two leavepieces were very similar.

PANEL RULING

General comments: The Panel noted that the Code permitted certain activities prior to the grant of the marketing authorization. The supplementary information to Clause 3 stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion prohibited by Clause 3 or any other clause.

In the Panel's view the closer to the grant of the marketing authorization for a product the more difficult it was to argue that activities were the legitimate exchange of medical and scientific information during the development of a medicine and not promotion.

The definition of promotion in Clause 1.2 did not include replies made in response to individual enquiries from members of the health professions or in response to specific communications whether of enquiry or comment, including letters published in professional journals, but only if they related solely to the subject matter of the letter or enquiry, were accurate and did not mislead and were not promotional in nature. Genuine unsolicited requests could be answered in a number of ways. In some instances it could be by simply sending the papers; in this regard Clause 1.2 of the Code described a reactive rather than a proactive role. Statements relating to human health or diseases were also exempt from the definition of promotion provided there was no reference either direct or indirect to specific medicines.

In the Panel's view it was not necessarily unacceptable for companies to have employees focussing on the provision of information prior to the grant of the marketing authorization. The arrangements and activities of such employees had to comply with the Code. Such employees should be comprehensively briefed about the Code. The area

was difficult and companies needed to ensure that the arrangements and activities were very carefully controlled and managed. The importance of documentation and instruction could not be overestimated.

The Panel noted that Abilify was not licensed in the UK. It appeared that Bristol-Myers Squibb and Otsuka were using medical representatives to provide information to health professionals ahead of launch.

* * * * *

In considering the allegations regarding the two leavepieces 'Achieving a Balance' and 'Achieving Stability' (points A1 and A2) the Panel also bore in mind the allegation and response in relation to representatives' training (point A3) as the Panel considered that the use of the leavepieces as well as their content were relevant factors. The leavepieces were used by medical representatives as part of introductory discussions focussing on ligand-receptor interactions.

The Panel noted that the leavepiece, 'Achieving a Balance' did not mention a product by either brand name or generic name. It featured a large illustration which was an artist's impression of the receptor binding of agonists, antagonists, and partial agonists. The leavepiece was referenced to Tamminga which discussed partial dopamine agonists in the treatment of psychosis and referred to aripiprazole. The back page of the leavepiece gave details of useful contacts; three of the four contacts stated were mental health charities, two of which were linked particularly with schizophrenia. In the Panel's view the cited reference and the list of contact details gave an implied reference to an antipsychotic medicine.

The Panel noted the role of representatives. It considered that overall the features the representatives were to discuss with health professionals were closely associated with Bristol-Myers Squibb and Otsuka's forthcoming product, Abilify. Overall the Panel considered that such activity did not constitute the legitimate exchange of medical or scientific information during the development of a product and went beyond the provision of corporate information about an area of research. The leavepiece formed an integral part of the information provided by representatives, which when considered in its totality was, in the Panel's view, associated with Abilify which did not have a marketing authorization. The leavepiece and its provision by the representatives in this context amounted to a breach of Clause 3.1 of the Code and the Panel ruled accordingly. The Panel did not consider that the leavepiece was disguised; it would not be seen as anything other than a promotional item. The Panel thus ruled no breach of Clause 10.1.

2 Leavepiece 'Achieving Stability'

The leavepiece (ref ABI/08-03/0178/07-05 as provided by Bristol-Myers Squibb and Otsuka) consisted of four pages and discussed the activities of agonists, antagonists and partial agonists in relation to the hypoactive and hyperactive system.

COMPLAINT

Lilly stated the inside double-page spread showed graphs indicating how full agonists, antagonists and partial agonists might act in the setting of a hypoactive system and a hyperactive system. The back page stated, beneath a heading 'Stabilising Activity', that agonists were effective in a hypoactive system, antagonists were effective in a hyperactive system and that partial agonists had the overall ability to reduce activity in a hyperactive system and to increase activity in a hypoactive system. The statements were referenced to Stahl (2001) which described the mode of action of aripiprazole. Since a major activity of the joint marketing arrangement between Bristol-Myers Squibb and Otsuka was to commercialise aripiprazole, and since the joint venture had no other marketed products relevant to the messages in the leavepiece, it was difficult to see how the leavepiece, issued in the names of both companies and describing known properties of aripiprazole (which was the first antipsychotic recognised to be a partial agonist at the time of its launch anywhere in the world) could be used other than to prompt or solicit a request for information about aripiprazole. Lilly alleged that the leavepiece was disguised promotion of aripiprazole in breach of Clause 10.1 of the Code and was designed to promote a medicine prior to the grant of a marketing authorization in breach of Clause 3.1.

RESPONSE

Bristol-Myers Squibb and Otsuka stated that the leavepiece as quoted by Lilly ABI/08-03/0128/07-05 did not exist. The companies considered that Lilly must be referring to the leavepiece ref ABI/08-03/0178/07-05 which was withdrawn several months ago. It also contained only scientific information about ligand-receptor interactions. Aripiprazole was not mentioned in the document. Given this the leavepiece could not be seen as promotional there could be no breach of Clauses 3.1 or 10.1 of the Code.

PANEL RULING

The Panel noted its general comments in point A1 above. The 'Achieving Stability' leavepiece was to be used by representatives for three months following the use of the leavepiece 'Achieving a Balance' at issue in point A1. The Panel noted that the leavepiece 'Achieving Stability' did not mention a product by either brand name or generic name. The leavepiece compared the action of agonists, antagonists and partial agonists. More detail regarding the activity of these products was provided than in the leavepiece considered at point A1. The leavepiece now in question was referenced to Stahl which was entitled 'Dopamine System Stabilizers, Aripiprazole and the Next Generation of Antipsychotics'. No details of useful contacts were given. The Panel considered that the leavepiece 'Achieving Stability' and its provision by representatives within the context described at point A1 amounted to the promotion of Abilify prior to the grant of the marketing authorization. A breach of Clause 3.1 was ruled. The Panel did not consider that the leavepiece was disguised; it would not be

seen as anything other than a promotional item. The Panel thus ruled no breach of Clause 10.1 of the Code.

3 Representative training

COMPLAINT

Lilly recognised that although partial agonists that were not antipsychotics might be used to treat anxiety, Parkinson's disease and cardiovascular diseases, the references used in support of the two leavepieces (points A1 and A2) clearly related only to psychosis and emphasised to a great extent that partial dopamine agonists might represent the next new class of antipsychotics. Furthermore the leavepieces were obtained from a Bristol-Myers Squibb stand at a meeting in Edinburgh 30 June – 3 July which clearly stated 'The Road to the Future of Atypicals'. Medical representatives manned the stand and at least two leavepieces were given out with the same colour scheme/background as the stand livery or branding. Lilly could not accept it credible that the theme of the leavepieces could relate to any other partial agonist other than an atypical antipsychotic. Bristol-Myers Squibb and Otsuka were also highly unlikely to be engaging in any activity that related to amisulpride, the only current atypical antipsychotic that was recognised to have possible partial agonist properties.

Lilly believed the two leavepieces were being used as detailing materials by Bristol-Myers Squibb and/or Otsuka representatives. Lilly considered that it would be difficult for representatives to maintain credibility when talking to psychiatrists about the matters described in the two leavepieces if they had not been trained or otherwise informed about the pharmacological properties of aripiprazole. Clearly training representatives about aripiprazole would not be necessary prior to the grant of a marketing authorization if those representatives were not being encouraged to promote the medicine prior to the grant of a marketing authorization. For this reason Lilly alleged that Bristol-Myers Squibb and/or Otsuka had also breached Clause 15.9 of the Code by encouraging an action which would be in breach of the Code.

In discussions with Bristol-Myers Squibb/Otsuka, Lilly had been told that their representatives had not been trained on aripiprazole. On a medical information request form (that specified the product aripiprazole) there was a name given as a representative of Bristol-Myers Squibb with a Bristol-Myers Squibb email address and the territory number and mobile telephone number. It was unclear as to why the name and contact details (that included only a mobile telephone number and not the head office or medical information number) needed to be included on this form. Lilly again believed that it would be difficult for representatives to maintain credibility when receiving such requests for information from psychiatrists if they had not been trained or otherwise informed about the pharmacological properties of aripiprazole. Clearly training representatives about aripiprazole would not be necessary prior to the grant of a marketing authorization if those representatives were not being encouraged to promote the medicine prior to the grant of a marketing authorization. For this reason Lilly alleged that Bristol-Myers Squibb and/or Otsuka had also breached Clause 15.9 of the Code by encouraging an action which would be in breach of the Code.

RESPONSE

Bristol-Myers Squibb/Otsuka stated that the role of the representatives was to introduce themselves and the companies' heritage in this therapeutic area; to gain information on the local mental healthcare environment; to establish relationships and finally to have introductory discussions focusing on ligand-receptor interactions. The representatives were verbally briefed in relation to the objectives mentioned above. For the scientific section they were briefed using slides entitled 'Partial Agonism'. No standard set of questions was given to the representatives to ask.

The Bristol-Myers Squibb/Otsuka partnership currently existed solely for the development of aripiprazole. Fifty two representatives were initially employed by Bristol-Myers Squibb/Otsuka in anticipation of the launch of aripiprazole in April 2003. However the final positive opinion from the Committee for Proprietary Medicinal Products was received later than the companies had originally expected (February 2004).

The companies now had a dedicated CNS team in anticipation of launch in May. However during 2003 this team was re-deployed to spend the majority of its time selling Lipostat (pravastatin), Aprovel (irbesartan), Pletal (cilostazol) and Plavix (clopidogrel) to cardiologists and vascular surgeons.

Representatives did not promote licensed medicines in their meetings with mental health professionals.

The detail aid (ref ABI/04-03/0125/03-05) was used to discuss general ligand-receptor interactions in an educational context. The briefing for the detail aid was the same briefing as for the 'Achieving a Balance' leavepiece.

The leavepieces (points A1 and A2) had been used to provide background information on ligand-receptor interactions as mentioned in the briefing of May 2003. During that specific briefing the educational aspect of the medical representatives' role was highlighted. Clause 3.1 of the Code was quoted to make clear and to ensure medical representatives behaved professionally and in compliance with the Code.

Given that no training of representatives had taken place on aripiprazole and that all representatives were made fully aware of the Code the companies submitted that there was no breach of Clause 15.9 of the Code.

The stand at the meeting of the in Edinburgh made general reference to developments in the area of neuroscience. Although the word atypical was mentioned, the stand did not make any claim about any individual medicine. None of the people manning the stand was permitted to mention the compound or answer questions about it. Only two representatives were present at the meeting and neither was permitted to mention aripiprazole or

answer questions about it. In addition to the two leavepieces, request forms for further medical information were available to health professionals. This, therefore, could not constitute a breach of the Code. The two leavepieces (points A1 and A2) were available on the stand.

With regard to the allegation that the two leavepieces were being used as detailing materials by Bristol-Myers Squibb and Otsuka representatives, Lilly, however, was unable to produce any *prima facie* evidence. Bristol-Myers Squibb and Otsuka representatives were trained only in the disease area and were not trained specifically on aripiprazole. Given that there had been no training of Bristol-Myers Squibb or Otsuka representatives on aripiprazole and that Lilly had failed to produce any evidence to the contrary, Bristol-Myers Squibb and Otsuka submitted that there could be no ruling of a breach of Clause 15.9 of the Code.

With regard to the medical information request form, Bristol-Myers Squibb and Otsuka reiterated that medical representatives had not received any training on aripiprazole. When a medical representative received an unsolicited question about aripiprazole they had been instructed to refer the health professional to Bristol-Myers Squibb's medical department using the medical information request form. For solely administrative purposes (eg medical information might not be able to read handwriting), medical representative contact details appeared on the form. Doctors were not encouraged to contact the representative directly. The fact that the representative's name appeared on the form (for administrative reasons) was not *prima facie* evidence that training to promote aripiprazole had taken place. No breach of Clause 15.9 had occurred.

PANEL RULING

The Panel noted that the representatives had received four training modules as part of the 'Arpiprazole Learning System'. These were entitled 'Introduction to Mental Illness and Mental Health Care', 'Neuroanatomy and Neurophysiology', 'Disease States, Diagnosis and Treatment', and 'The Competition'. The modules did not feature on aripiprazole in detail but references were made to the product including benefits compared to atypical antipsychotics currently on the UK market.

Other training material consisted of four slide presentations, 'Partial Agonism', 'The Competition', 'CNS Business Unit Meeting Cycle 2' dated 15 May 2003 and 'CNS National Conference Bahamas' dated 10 September 2003.

The two CNS business unit presentations were made up of a number of slides each bearing what appeared to be the Abilify product logo. Each presentation referred to the ROAR programme (Receptor Occupancy and Activity Revision). The presentation dated 15 May 2003 included a slide headed 'Critical Success Factors' which instructed representatives to 'Consistently differentiate Abilify as "next generation atypical" emphasising efficacy at every opportunity', 'Drive awareness and enthusiasm across the customer base to ensure rapid uptake at launch' and 'Build relationships with customers of influence to ensure product endorsement'. The subsequent presentation dated 10 September reviewed the ROAR programme and listed the messages psychiatrists had heard associated with Abilify as 'Next generation atypical, superior tolerability and safety, unique mode of action, robust efficacy, partial agonism'. One slide referred to psychiatrists' sources of information on Abilify/aripiprazole followed by a bar chart which listed sales representatives as 49% and convention/conference as 26% (July 2003 data). Another slide stated that the ROAR II Rationale objectives included 'partial agonism MUST be perceived as a basis for unrivalled efficacy'.

The Panel noted that only the presentation on 15 May included any reference to the Code and that was in one slide which referred to the supplementary information to Clause 3.1 'Advance Notification of New Products or Product Changes'.

The slide presentation 'The Competition' (undated) identified current opportunities and the market situation. Details were given about the strengths and weaknesses of different treatments including Lilly's product Zyprexa. The weaknesses listed for Zyprexa included 'weight gain', 'risk of diabetes' and 'risk of dyslipidaemia'. A section headed 'unmet needs' referred to the high risk of weight gain, sedation, dyslipidaemia and diabetes. One slide stated that physicians needed medicines which did not raise concerns about obesity, diabetes and elevated lipids or cardiovascular problems among other things. Another slide stated that patients needed medicines that did not interfere *inter alia* with body weight, alertness and energy.

The slide set 'Partial Agonism' did not mention Abilify. It explained how partial agonism worked in relation to neurotransmitters and referred to partial agonism as a potential solution to complex diseases where neurotransmitter levels might simultaneously be too high in one area of the brain and too low in another area.

The Panel considered that the four slide presentations would encourage the representatives to promote Abilify to health professionals. Psychiatrists' sources of information on Abilify listed representatives as 49% (July 2003), an increase of 13% from March 2003. The role of a medical representative would be seen by the health professionals as promotional. The representatives were encouraged to discuss what, on the launch of Abilify, would be competitor products. Criticising competitor products was a promotional activity.

The Panel did not accept Bristol-Myers Squibb and Otsuka's submission that the representatives had not been trained on Abilify. Further the Panel queried whether any medical representative would receive a genuine unsolicited question about aripiprazole given their role, their training and the materials to be used by them.

None of the materials placed the activities in context. The Panel considered that the representatives' training material would lead to the promotion of an unlicensed medicine. The Panel therefore ruled the briefing material in breach of Clause 15.9 of the Code.

With regard to the medical information request form the Panel did not consider that including the representative's details on the form was itself a breach of the Code as alleged and on this narrow point no breach of Clause 15.9 of the Code was ruled.

B Meetings

During its consideration of the following allegations the Panel bore in mind its comments and rulings in points A1, A2 and A3 above.

1 Programme of ROAR lectures

Two meetings entitled 'Receptor Occupancy and Activation Review (ROAR)' were referred to by Lilly.

COMPLAINT

Lilly had obtained invitations to two ROAR lectures. One meeting was held in Leeds on 1 October 2003 for which arrangements appeared to have been made by a public relations (PR) agency. A similar meeting was held in Wales on 13 October 2003, also organised by a PR agency. The invitation for the Leeds meeting included a reply paid card that would be mailed back to the agency involved. The invitation also contained the name of a representative who was to be contacted for more information. This was the same person named on the medical information request form referred to in point A3 above.

The topic of the meetings was 'Receptor Occupancy and Activation Review'. According to the invitations the talks focused on the receptor pharmacology of atypical antipsychotics. It seemed likely that the talks would include mention of aripiprazole, and that, given the novelty of the concept, they would promote discussion about aripiprazole. The two companies, acting jointly, appeared to have used their PR agency (with the aid of a company representative) to invite doctors to hear a lecture touching on aripiprazole, a product that did not have a marketing authorization, for the purposes of soliciting a discussion with those doctors about aripiprazole. Lilly alleged that this constituted the marketing or promotion of a medicine prior to the grant of its marketing authorization in breach of Clause 3.1 of the Code.

RESPONSE

Bristol-Myers Squibb and Otsuka stated that the two ROAR lectures referred to were part of a medical education programme for the exchange of medical and scientific information on the dopamine hypothesis of schizophrenia, and the management of schizophrenia. These lectures were peer-to-peer meetings organised through a PR agency supported by Bristol-Myers Squibb and Otsuka. The lectures referred to agonists, antagonists and partial agonists as well as other management approaches. A total of eighteen ROAR lectures had taken place.

In order to ensure that balanced information was provided, distinguished academics were chosen as lecturers. The audiences were restricted to small number of attendees, generally academics and/or members of teaching and/or university hospitals.

There were thirty-six attendees at the Leeds meeting and nineteen attendees at the Wales meeting. Bristol-Myers Squibb/Otsuka medical representatives were involved in the logistics but did not attend the lectures. A representative's name was included on the invitation in case the health professional required more information on the logistics of the meeting. As the representatives were not trained to promote aripiprazole the health professional would not have been able to obtain product specific information from the person named. The representatives had no further role other than logistical and therefore no briefing was undertaken. Members of the medical department attended the ROAR lectures.

The invitations, speaker brief and slides were provided. The leavepieces referred to in points A1 and A2 above were also used at the meeting.

The companies submitted that the format of this meeting was clearly educational, not promotional. The speakers mentioned aripiprazole but in the context of a range of other treatments of schizophrenia. It was necessary for the compound to be mentioned briefly simply as an example of partial agonism. Other compounds were also mentioned to illustrate scientific points in a similar manner.

Given the purely educational nature of the meeting and that aripiprazole was not specifically the subject under discussion no breach of Clause 3.1 could have occurred.

In response to a request for further information, Bristol-Myers Squibb and Otsuka stated delegates to the ROAR lectures were selected on the basis of their perceived interest in neurotransmitters in schizophrenia.

PANEL RULING

The Panel noted that the invitation stated that the lecture would focus on the important role that receptor pharmacology played in the battle to effectively treat serious mental illness. The lecturer would examine what made an atypical antipsychotic atypical and would review the clinical implications. The lecturer for the Leeds meeting and the two lecturers for the Wales meeting were from the Institute of Psychiatry.

One set of slides provided gave an overview of the role of dopamine in schizophrenia including the relationship between receptor occupancy, extra-pyramidal side effects (EPS) and response.

Mechanisms of atypicality were discussed and aripiprazole was referred to as a potent partial agonist at certain dopamine receptors. The impression was given that a dopamine partial agonist caused less EPS than haloperidol. One of the conclusions was that a dopamine partial agonist might offer a way of targeting both dopaminergic deficits and stabilize the system.

The Welsh slides included details about neurotransmission and the dopamine hypothesis of schizophrenia as well as information about 5-HT receptors. Copies were provided.

The Panel noted that one of the objectives for the peer-to-peer regional meetings in the representatives'

briefing material was to 'Continue the positive cascade of anticipation for Abilify'.

The Panel noted that the stand and material available at the meeting were similar to those at issue in points A1, A2 and A3 above.

The Panel considered that the meetings organised by Bristol-Myers Squibb and Otsuka amounted to a marketing exercise designed to raise awareness of aripiprazole and to raise expectations that the new product might meet some of what were seen as problems with currently licensed medicines.

The Panel considered that the ROAR lectures constituted promotion of Abilify prior to the grant of its marketing authorization and thus ruled a breach of Clause 3.1 of the Code.

2 Meeting at the Royal College of Psychiatry 30 June – 3 July

COMPLAINT

Lilly stated that Bristol-Myers Squibb and Otsuka had a stand at this meeting with exhibition panels carrying the clear statement 'The Road to the Future of Atypicals'. The stand was manned by medical representatives and at least two leavepieces were given out with the same colour scheme/background as the stand livery or branding. The contents of the leavepieces made it clear that the medicine, which would be the future atypical, was aripiprazole. It was difficult to see how the messages disseminated in the names of both companies and describing known properties of aripiprazole (which was the first partial agonist antipsychotic licensed anywhere in the world) could be intended other than to prompt or solicit a request for information about aripiprazole. Lilly alleged that the exhibition panels were disguised promotion of aripiprazole in breach of Clause 10.1 of the Code and were designed to promote a medicine prior to the grant of a marketing authorization in breach of Clause 3.1.

RESPONSE

Bristol-Myers Squibb and Otsuka stated that many of the issues raised here by Lilly had been addressed above. To reiterate, however, no medicine was mentioned on the stand. Lilly claimed that the leavepieces (points A1 and A2) made it clear that the medicine was aripiprazole. Neither the stand nor the leavepieces mentioned the medicine. A health professional would have had to have searched extensively to determine that the medicine was aripiprazole. Indeed, the obtaining of a full text version of an article followed by detailed reading of it would suggest that the disputed link was far from clear. Given that there was therefore no disguised promotion of aripiprazole at this meeting and therefore no marketing before the granting of a marketing authorization there could be no breach of Clauses 10.1 and 3.1 of the Code.

PANEL RULING

The Panel noted its comments and rulings upon the provision of the leavepieces, the ROAR programme, the role of representatives and their training at points A1, A2, and A3 above. The Panel noted that the exhibition panels clearly related to a future atypical antipsychotic which would be available from Bristol-Myers Squibb and Otsuka. The Panel considered that the companies' activities went beyond the exchange of medical and scientific information during the development of a medicine. The Panel considered that the exhibition panels amounted to the promotion of Abilify prior to the grant of its marketing authorization; a breach of Clause 3.1 of the Code was ruled. The Panel did not consider that the exhibition panels were disguised; they would not be seen as anything other than promotional. The Panel thus ruled no breach of Clause 10.1 of the Code.

3 Other meetings

COMPLAINT

Lilly stated that other locations of meetings organised or sponsored by Bristol-Myers Squibb/Otsuka at which promotional stands and other marketing paraphernalia were prominently displayed included a large advisory meeting for 200 customers from around the UK and Ireland who were flown to Manchester in the spring of 2003. Lilly had received additional anecdotal reports that a claim was being made that Zyprexa was associated with an increased risk of diabetes that differed significantly from either existing compounds or from aripiprazole. This message was being disseminated despite the recent comparative data produced by Bristol-Myers Squibb and published by the Food and Drug Administration (FDA) on its website which showed that this was not so. A specific example was the question 'Does a link between olanzapine and diabetes concern you and adversely affect your prescribing?' asked of an audience of around 80 consultants invited to a meeting in Newcastle in 2003. These doctors were invited to vote either yes or no.

These further instances of disguised promotional meetings and detailing by Bristol-Myers Squibb and/or Otsuka representatives supported Lilly's view that at least some Bristol-Myers Squibb or Otsuka representatives were actively promoting aripiprazole to doctors (other than service planners or budget holders) prior to the grant of a marketing authorization in breach of Clauses 3.1 and 15.1 and suggested that that they had been trained to do so in breach of Clauses 3.1 and 15.9.

Lilly stated that Bristol-Myers Squibb/Otsuka had to date been unable to show that it had received specific requests for suitably qualified members of its medical department to attend and give written or orally presented scientific information at the hospitals referred to above.

RESPONSE

Bristol-Myers Squibb and Otsuka stated that a meeting took place Manchester on 8 July 2003, as part of the ROAR programme, and was attended by 18. The invitation was provided. The briefing materials

and slides were the same as the two ROAR meetings considered in point B1 above.

The question regarding the link between olanzapine and diabetes had not been asked at any meeting. Lilly appeared to have based this allegation on belief and not evidence.

Bristol-Myers Squibb and Otsuka's standard procedure was to review and approve all presentations shown at meetings in advance. Care was taken to ensure that accurate, balanced and fair information was presented. The companies did not seek to disparage competitors' products.

Given the lack of *prima facie* evidence and the anecdotal and unsubstantiated nature of the allegations made by Lilly there could be no breach of Clauses 3.1, 15.1 or 15.9.

In relation to the allegation that Lilly had received reports that claims were being made that Zyprexa was associated with an increase in risk of diabetes the companies submitted that on January 26, a joint panel from the American Diabetes Association, the American Psychiatric Association, and the North America Association for the Study of Obesity published a recommendation from a consensus conference held in November 2003 on antipsychotics, obesity, and diabetes. This independent body reviewed the effect of second generation antipsychotics on, *inter alia*, the onset of diabetes. It concluded that the data demonstrated that there was a consistent increased risk for diabetes in patients treated with olanzapine which had not been shown with aripiprazole. As the recommendation was in the public domain and had triggered an international debate within psychiatry, the companies thought it was important to specifically tell its medical representatives not to engage psychiatrists in discussion around this publication or these side effects. If they received an unsolicited question about this recommendation they were instructed to state that as aripiprazole was an unlicensed product, they were not in a position to answer the question. The physicians were then referred to the medical information department.

Bristol-Myers Squibb and Otsuka believed that this internal briefing document confirmed their willingness to adhere to the Code. It also confirmed that they ensured balanced information was provided to medical representatives and that the competition was not disparaged in contravention of the Code.

PANEL RULING

The Panel noted that a meeting for 18 delegates had taken place on 8 July 2003 in Manchester. This was part of the ROAR programme. The Panel considered that this meeting was covered by its general rulings about the ROAR programme set out in point B1 above.

The Panel considered that the general allegation that the companies' representatives were actively promoting aripiprazole prior to the grant of its marketing authorization, or had been trained to do so, was already covered by the Panel's comments and rulings at point A3 above.

The Panel noted that with regard to the allegation about what was said in relation to Zyprexa and diabetes, no clauses of the Code had been cited. It was thus not able to make a ruling in this regard. However it noted its comments made in relation to a similar allegation where no *prima facie* case to answer had been ruled. These being that references to licensed products appeared in the training and briefing material. With regard to Zyprexa, diabetes was given as an adverse effect, its associated risk of causing diabetes was described as a disadvantage and the risk of diabetes was described as a weakness. Training module 4 'The Competition' included a table indicating that the relative occurrence of diabetes was between 'infrequently seen' and 'commonly seen'. The Panel noted that the Zyprexa summary of product characteristics (SPC) stated in Section 4.4 Special warnings and precautions for use that hyperglycaemia and/or development or exacerbation of diabetes, occasionally associated with ketoacidosis or coma had been reported very rarely including some fatal cases. Further that in some cases a prior increase in body weight had been reported which might be a predisposing factor. The Panel considered that Bristol-Myers Squibb and Otsuka's briefing material did not reflect the information in the Zyprexa SPC. The briefing material overall implied that Zyprexa caused diabetes. The Panel was concerned whether the briefing material complied with Clause 15.9 of the Code as it would be likely to lead to a breach of the Code. The Panel requested that Bristol-Myers Squibb and Otsuka be advised of its views.

4 Advisory Board meetings

COMPLAINT

Lilly stated that it had recently been told by a nurse in Manchester that he was invited to an advisory board meeting that took place in Manchester in the autumn of 2003. He recalled there being around 50 people present and could name at least one other nurse present. The purpose of the meeting appeared to have been for the advisory board to give advice and comment on some proposed marketing materials that related to aripiprazole. He recalled that these materials were handed out and then collected at the end of the meeting. He further recalled that this meeting was one of a series of maybe four similar such meetings. Payment was made to the attendees.

These further instances of disguised promotional meetings and detailing by Bristol-Myers Squibb and/or Otsuka representatives supported Lilly's view that at least some Bristol-Myers Squibb or Otsuka representatives were actively promoting aripiprazole to nurses (other than service planners or budget holders) prior to the grant of a marketing authorization in breach of Clauses 3.1 and 15.1 and suggested that that they had been trained to do so in breach of Clauses 3.1 and 15.9.

RESPONSE

Bristol-Myers Squibb and Otsuka stated that between August and December 2003 its medical departments had run 10 regional advisory panels. Representatives

did not attend these meetings. There were 6-12 attendees at each meeting the objectives of which were to get an understanding of the regional mental health environment and to get feedback from key national and regional psychiatrists on the current treatment and management of schizophrenia. The meetings were held in the late afternoon and attendees were paid a £500 honorarium. All attendees signed confidentiality agreements.

Advisory boards were an essential part of understanding a disease area, were non promotional and an accepted method of gauging the external environment and opportunities in the future.

The companies stated that Lilly had no evidence to support its view that the meetings were disguised promotion by trained representatives and thus no breach of Clauses 3.1 and 15.9 could be ruled.

The invitation, agenda, and slides were provided.

Neither Bristol-Myers Squibb nor Otsuka had made the claims alleged by Lilly. In addition to this Lilly had failed to provide any evidence that the contrary was true.

In response to a request for further information, Bristol-Myers Squibb and Otsuka stated that health professionals were informed about payment for advisory board meetings via a letter, sent out after the advisory board.

Selection of attendees for the advisory boards was based on the understanding that they were recognized local opinion leaders who would help the companies to understand regional variations in the mental health environment. All attendees participated in workshops to facilitate an understanding of the current management of schizophrenia.

PANEL RULING

The Panel noted that there was a difference between Lilly's description of the advisory board meeting and that of Bristol-Myers Squibb and Otsuka.

Bristol-Myers Squibb and Otsuka stated that 10 advisory boards had been run with a maximum of 12 persons per advisory board. The invitation to the meeting on 31 July 2003 stated that the companies were convening the advisory board to seek counsel on the current issues surrounding the UK antipsychotic market and to evaluate the aripiprazole data from a UK perspective. Input on the launch of the product to both primary and secondary care would be sought. The invitation also stated that as a follow up the companies anticipated working with some individual members beyond the advisory board meetings. The meetings commenced at 3.30pm (registration from 3pm) and closed at 7pm followed by dinner. The agenda consisted of three presentations; 'mental health environment', 'mechanism of action and efficacy' and 'tolerability'. In addition there were workshop breakouts and coffee for 45 minutes and discussion of patient types for 45 minutes. It appeared from the agenda that some sessions would be run by medical personnel and others by marketing.

The slides provided by Bristol-Myers Squibb and Otsuka consisted of two presentations, 'Aripiprazole Next Generation Atypical Antipsychotics' and 'Aripiprazole Advisory Panel Meeting'. Each of the slides was branded with what appeared to be the Abilify logo. The 'Aripiprazole Next Generation…' presentation focussed on its 'unique partial agonist mode of action', 'excellent long-term efficacy', stated that it was 'very well tolerated,' and gave results from a study in the US and its use in the US. The final slide listed three topics for discussion; whether the data linked the mode of action of aripiprazole with its efficacy and tolerability profile, what gaps should be addressed, and based on the product's profile asked what the main opportunities were.

The 'Aripiprazole Advisory Panel Meeting' presentation included the following list of objectives: 'Validate market research findings, particularly in the area of customer insight and motivation to prescribe; use real-life experiences to understand degree and comfort of using a new anti-psychotic; understand whether aripiprazole is perceived as the latest atypical or the first in a new class and test the sufficiency of the aripiprazole data set'.

The Panel considered that the slides were promotional as they included very strong claims for the product. It did not appear that the companies were asking for views on how the product should be promoted.

The Panel accepted that there was a difference between holding a meeting for health professionals and employing health professionals to act as consultants to a company. In principle it was acceptable for companies to pay health professionals and others for advice as to how their products should be promoted. The arrangements had to comply with the Code.

The Panel noted the companies' submission that the purpose of the meeting was to understand the regional mental health environment and to get feedback from key national and regional psychiatrists on the current treatment and management of schizophrenia. The invitation also referred to the evaluation of aripiprazole data from a UK perspective.

The Panel considered that although the invitation mentioned the interactive nature of the meeting, it was not sufficiently clear about the precise role of the invitees in that no mention was made of the £500 payment per attendee. The invitation referred to a form which was not provided. The agenda did not allow much time for feedback from the participants. No pre-reading/work was required. The £500 payment per attendee seemed high for the amount of work done. Ten regional meetings were to be held and the Panel queried whether there was sufficient justification for the number of meetings held. It was not clear how the potential delegates had been selected. The delegates were being 'employed' as consultants and as such their selection should stand up to independent scrutiny.

In the Panel's view it was questionable whether all the delegates would have truly acted as consultants to the companies each giving such advice as to justify a £500 honorarium. The Panel considered that it was untenable to argue that the delegates were being employed for their views when the delegates were only informed about payment after the meeting.

The Panel was concerned about the wording of the invitation, the number of meetings held, the materials presented at the meeting and that it was not clear what was expected from the participants. The Panel considered that the arrangements for the advisory board meetings were unacceptable, they constituted a series of promotional meetings for Abilify which was not licensed in the UK. The Panel ruled a breach of Clause 3.1 of the Code.

The Panel considered that as the meetings were deemed promotional it was unacceptable to pay attendees. Such an allegation would usually be considered in relation to Clause 18.1 of the Code but this had not been cited by Lilly. The Panel thus could not make such a ruling but requested that Bristol-Myers Squibb and Otsuka be advised of its views.

The Panel noted Bristol-Myers Squibb and Otsuka's submission that representatives had not attended the advisory board meetings. The Panel considered that on the evidence before it the representatives had not promoted Abilify at the advisory board meetings and thus ruled no breach of Clauses 15.1 and 15.9 of the Code.

C Alleged breach of Clauses 9.1 and 2

COMPLAINT

Lilly alleged that Bristol-Myers Squibb and/or Otsuka had failed to maintain high standards in breach of Clause 9.1. Further the companies had brought the industry into disrepute in breach of Clause 2 by the extensive promotion of an unlicensed medicine prior to the grant of the marketing authorization.

RESPONSE

Bristol-Myers Squibb and Otsuka stated that the complaints raised by Lilly had largely been made as a result of unsubstantiated reports that were unfounded and the companies were concerned that a complaint of this kind should have been made with such a lack of *prima facie* evidence after a delay of more than four months.

Bristol-Myers Squibb and Otsuka submitted that they had acted at all times in accordance with the Code and particular care was taken to ensure that at any meeting accurate, balanced and fair information was presented. The companies did not seek to disparage competitors' products.

Moreover, neither Bristol-Myers Squibb nor Otsuka would encourage any action which would be in breach of the Code and had at all times sought to maintain both the highest standards of conduct, and also the reputation of the industry as a whole. The companies refuted all the allegations made by Lilly.

PANEL RULING

The Panel noted its rulings of breaches of the Code. It considered that neither Bristol-Myers Squibb nor Otsuka had maintained high standards and thus each was ruled in breach of Clause 9.1.

The Panel noted that Clause 2 was used as a sign of particular censure and was reserved for such use. The Panel considered that Bristol-Myers Squibb and Otsuka's activities brought discredit upon and reduced confidence in the pharmaceutical industry. Each company was ruled in breach of Clause 2 of the Code.

The Panel was concerned about the nature and scale of the activities. It thus decided to report Bristol-Myers Squibb and Otsuka to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

COMMENTS FROM BRISTOL-MYERS SQUIBB AND OTSUKA

The companies returned the requisite undertakings and assurances. At the consideration of the report the representatives acknowledged that there had been a series of misjudgements and that they had little experience with pre-launch activities. Both companies had reviewed procedures relating to the Code. Amendments had been made to standard operating procedures (SOPs).

APPEAL BOARD CONSIDERATION

During the consideration of the report the Appeal Board noted that the applications for Abilify licences in the US and in Europe were submitted at about the same time. The US licence was granted in November 2002 following FDA accelerated approval. European approval was anticipated in December 2002 but the Committee for Proprietary Medicinal Products (CPMP) asked for additional information on a number of occasions.

The delayed marketing authorization for Abilify had meant that representatives had had to sell other products which were licensed; they had also worked as 'information gatherers' using the two leavepieces 'Achieving a Balance' and 'Achieving Stability' for about 8 months. The companies had accepted that their actions had amounted to the promotion of Abilify prior to the grant of its marketing authorization. The Appeal Board decided that in accordance with Paragraph 10.4 of the Constitution and Procedure, Bristol-Myers Squibb and Otsuka should each be required to undergo audits of their procedures relating to the Code of Practice.

Upon consideration of the audit reports the Appeal Board noted that progress had been made which must continue. These cases concerned a serious matter. Taking all the circumstances into account it decided that the companies should be re-audited in six months' time (March 2005).

Complaint received **8 March 2004**

Undertaking received **13 May 2004**

Proceedings completed **8 September 2004**

PFIZER v ALLERGAN

Alleged disparagement of Pfizer

In Case AUTH/1516/9/03 Pfizer alleged that the provision by Allergan of ophthalmic slit lamps or educational grants to ophthalmologists in association with a Lumigan initiative was an inducement to prescribe and brought discredit upon the industry. The Panel ruled Allergan in breach of the Code and was so concerned about the arrangements that it reported the company to the Appeal Board. Upon receiving the report from the Panel, the Appeal Board required Allergan to write to each clinician to whom a slit lamp or educational grant had been supplied to request, where practicable, its return.

Pfizer stated that it had received several reports from centres across the UK that it was being disparaged by Allergan's representatives as they delivered the letters referred to above. Pfizer did not consider it acceptable that when, upon request, Allergan representatives discussed the ruling in Case AUTH/1516/9/03, they cast blame upon Pfizer.

The Panel noted that the Authority had not provided Pfizer with any information about the actions the Appeal Board required Allergan to undertake.

The Panel noted that Pfizer had not provided any substantive evidence to support its allegations. Allergan had provided copies of the letter requesting return of the slit lamps or educational grants, a briefing document about delivery of the letter and a short email which was sent to the representatives on the day after Allergan had accepted the Panel's rulings. The email began 'As you are all aware Pfizer have complained about [the Lumigan] initiative claiming it was a breach of the ABPI, an inducement to R_x'. Thereafter Pfizer was not mentioned either implicitly or explicitly. Neither the briefing document, nor the letter sent to clinicians made any reference to Pfizer. In answer to the question 'How could this happen?' the answer in the briefing document began 'This was an error on Allergan's part …'. The Panel did not consider that either the briefing document or the email advocated disparagement of Pfizer. No breach of the Code was ruled. There was no evidence before the Panel that disparagement of Pfizer had occurred and so the Panel ruled no breach of the Code.

In Case AUTH/1516/9/03 Pfizer Limited alleged that the provision by Allergan UK Limited of ophthalmic slit lamps or educational grants to ophthalmologists in association with a Lumigan initiative was an inducement to prescribe and brought discredit upon the industry. The Panel ruled Allergan in breach of the Code and was so concerned about the arrangements that it reported the company to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure. Allergan provided the requisite undertaking and assurance.

Upon receiving the report from the Panel, the Appeal Board, *inter alia*, was very concerned that a large number of clinicians might be left with the impression that the arrangements were acceptable. The Appeal Board required Allergan to take steps to recover the slit lamps and educational grants as set out in Paragraph 10.3 of the Constitution and Procedure. Allergan was required to write to each clinician to whom a slit lamp or educational grant had been supplied to request, where practicable, its return. These letters were seen by the Authority and hand delivered by Allergan's representatives.

COMPLAINT

Pfizer stated that it had received several reports from centres across the UK that it was being disparaged by Allergan's representatives as they delivered the letters referred to above. Pfizer had asked Allergan for clarification of the representatives' briefing regarding these letters as it considered that it might be in breach of Clause 15.9 of the Code. Pfizer did not consider it acceptable that when, upon request, Allergan representatives discussed the ruling in Case AUTH/1516/9/03, they cast blame upon Pfizer. Pfizer alleged that such activity was in breach of Clause 8.1 of the Code.

RESPONSE

Allergan noted that the letter at issue made no mention of Pfizer. Allergan submitted that its representatives were briefed beforehand, in writing and by telephone, about the appropriate delivery of the letters. Copies of the briefing document and of the final letter were provided to the Authority. No reference was made to Pfizer and there was no instruction to mention Pfizer in any way. Allergan submitted that its representatives were careful to stick to the text of the brief and acted in a professional manner at all times. Copies of the representatives' briefing document, an email to the representatives and the letter to clinicians were provided.

Allergan did not consider that the briefing given to its representatives was in breach of Clause 15.9 of the Code. The company strongly refuted the suggestion that its representatives had 'cast blame upon Pfizer' and was confident that they had acted appropriately, and had not disparaged Pfizer.

Allergan noted that clinicians occasionally asked its representatives who had complained and they responded as truthfully and factually as they could. This information was only given out in response to unsolicited enquiries, and was never volunteered.

Allergan took the suggestion that any of its representatives might have disparaged Pfizer very seriously and had asked Pfizer to provide details of any rogue representatives that might have acted in this way, so that the matter could be investigated and appropriate action taken. No such details had been provided.

Allergan was confident that its representatives had acted appropriately, and had not disparaged Pfizer. The company therefore denied a breach of Clause 8.1.

PANEL RULING

The Panel noted that the Authority had not provided Pfizer with any information about the actions the Appeal Board required Allergan to undertake. The Panel further noted that the letter at issue had not been pre-approved by the Authority as submitted by Allergan. The Authority had seen the letter and suggested amendments which had been accepted by Allergan.

The Panel noted that Pfizer had not provided any substantive evidence to support its allegations. Allergan had provided copies of the letter requesting return of the slit lamps or educational grants together with a briefing document about delivery of the letter and a short email which was sent to the representatives on the day after Allergan had accepted the Panel's rulings of breaches of the Code. The email began 'As you are all aware Pfizer have complained about [the Lumigan] initiative claiming it was a breach of the ABPI, an inducement to R_x'.

Thereafter Pfizer was not mentioned either implicitly or explicitly. Neither the briefing document, which, *inter alia*, explained the background to the case and provided some questions and answers, nor the letter sent to clinicians made any reference to Pfizer. The Panel noted that the briefing document did not even refer to the complaint. In answer to the question 'How could this happen?' the answer in the briefing document began 'This was an error on Allergan's part …'. The Panel did not consider that either the briefing document or the email advocated disparagement of Pfizer. No breach of Clause 15.9 was ruled. There was no evidence before the Panel that disparagement of Pfizer had occurred and so the Panel ruled no breach of Clause 8.1.

Complaint received **17 March 2004**

Case completed **23 April 2004**

CASE AUTH/1570/3/04 *NO BREACH OF THE CODE*

JANSSEN-CILAG/DIRECTOR v LILLY

Alleged breach of undertaking

Janssen-Cilag complained about Lilly's use of a poster (Roychowdhury *et al* 2004) which compared Zyprexa (olanzapine) with, *inter alia*, Janssen-Cilag's product Risperdal (risperidone). The data for the comparison of Zyprexa with risperidone was referenced to Tran *et al* (1997). The poster concluded that, using multiple definitions of response and relapse olanzapine was better at reducing relapse in patients with schizophrenia than the comparators.

As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

Janssen-Cilag noted that a Lilly press release relating to the poster prompted an article in Chemist & Druggist which included claims that patients on Zyprexa apparently relapsed less frequently than those receiving Risperdal. The article ended with the statement: 'For more information Lilly Medical Information Tel [number given]. In response to Janssen-Cilag's request for more information, but not specifically for the poster, a copy of the poster was volunteered and sent.

Janssen-Cilag noted that in Case AUTH/1325/5/02 Lilly had accepted the Panel's ruling of a breach of the Code with regard to claims for Zyprexa of superior efficacy compared with Risperdal in preventing relapse based on Tran *et al*. In that case the Panel had noted that Tran *et al* had not been designed to measure relapse rates. Janssen-Cilag thus assumed that claims of superior relapse prevention for Zyprexa compared to Risperdal based on the results of Tran *et al* were unacceptable and so it was surprised to have received the poster from Lilly as further information supporting the article in Chemist & Druggist, which contained such claims, when it had not been specifically requested.

Janssen-Cilag submitted that the conclusions of the poster were clearly misleading and used data previously ruled to be inappropriate to demonstrate comparative rates of relapse between Zyprexa and Risperdal. Medical information departments were subject to the Code and thus required to supply information that was not misleading, was balanced and represented an up-to-date evaluation of all the evidence. Hence, even if a medical information department was asked to supply a specific reference, it should not do so if it was misleading unless it pointed out the misleading element to the requester and attempted to provide a balanced view.

Janssen-Cilag alleged that supply and/or use of this poster by Lilly (regardless of whether it was from its medical information department) was failing to comply with a previous undertaking and so by consequence Lilly had not maintained the high standards expected of the pharmaceutical industry.

The Panel noted that Case AUTH/1325/5/02 concerned, *inter alia*, the claim 'Significant reduction in relapse rates compared to risperidone' referenced to Tran *et al*. The Panel had noted that the Tran paper had not referred to relapse rates. The primary objective of the study was to evaluate the effectiveness and safety of olanzapine versus risperidone during double-blind therapy. The maintenance of response as measured by Tran *et al* had only taken into account Positive and Negative

Syndrome Scale (PANSS) total score and Clinical Global Impression (CGI) score. In this regard, the Panel noted that in a study which had specifically examined relapse rates in patients with schizophrenia, relapse was defined by any one of 5 parameters (Csernansky *et al*). In the Panel's view Tran *et al* had not been designed to measure relapse rates; maintenance of response as defined by two parameters, was not the same as prevention of relapse. The Panel had considered that the claim did not accurately represent the findings of Tran *et al* and was misleading in that regard. A breach of the Code was ruled and accepted by Lilly.

Turning to the case now before it, Case AUTH/1570/3/04, the Panel noted that olanzapine and risperidone data from Tran *et al* had been used in the poster produced by Lilly USA. The poster concluded that, *inter alia*, olanzapine was better at reducing relapse in patients with schizophrenia than risperidone using different definitions of response and relapse. The Panel considered that the poster *per se* was not subject to the Code. It had been displayed in an academic forum organised by a third party. Lilly's use of the poster in the UK, however, must comply with the Code.

Lilly UK had issued a press release to medical journals entitled 'Zyprexa superior head-to-head to other atypicals in schizophrenia relapse-prevention' followed by 'Additional quality of life data shows Zyprexa benefits vs other atypicals may lead to better patient outcomes over time'. The press release referred to the new data (the poster) which demonstrated that Zyprexa-treated patients experienced significantly longer delays to schizophrenia-relapse in comparison to patients who received other leading atypical antipsychotics. The Panel noted its comments and rulings about the Tran data as detailed above. The press release also stated that Zyprexa-treated patients relapsed significantly less than Risperdal treated patients ($p \leq 0.001$).

The Panel noted that the Code stated that the term promotion did not include replies made in response to individual enquiries from members of the health professions or appropriate administrative staff or in response to specific communications from them whether of enquiry or comment, including letters published in professional journals, but only if they related solely to the subject matter of the letter or enquiry, were accurate and did not mislead and were not promotional in nature.

The Panel noted that the data in the poster relating to the comparison of relapse rates with Zyprexa and Risperdal had been taken from Tran *et al*. Lilly had accepted in Case AUTH/1325/5/02 that Tran *et al* was not designed to measure relapse rates.

The Panel considered that the press release and the poster were misleading with regard to the comparative efficacy of Zyprexa and Risperdal to prevent relapse in schizophrenia. The Panel considered that the press release and Lilly's use of the poster meant that the company had not complied with its undertaking; high standards had not been maintained. Breaches of the Code were ruled. The Panel also considered that by not complying with an undertaking Lilly had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled. These rulings were appealed by Lilly.

The Appeal Board noted the parties' submissions that there was no generally accepted definition of relapse in schizophrenia. The Appeal Board further noted that the source data which had formed the basis of Tran *et al* had been reanalysed and presented by Roychowdhury *et al*. It was not a reanalysis of the data produced by Tran *et al* but a reanalysis of the data used by that group in its comparison of olanzapine and risperidone. In the Appeal Board's view reanalysis of source data was a valid scientific methodology. The Appeal Board considered that Roychowdhury *et al* had applied sufficiently different definitions to those used by Tran *et al* such that use of the poster at issue did not represent a breach of the undertaking given in Case AUTH/1325/5/02. No breach of the Code was ruled. Consequently the Appeal Board also ruled no breach of Clause 2 of the Code.

Janssen-Cilag Ltd complained about Eli Lilly and Company Limited in relation to use of a poster (Roychowdhury *et al* 2004). The poster compared Zyprexa (olanzapine) with, *inter alia*, Janssen-Cilag's product Risperdal (risperidone).

As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

The poster was presented at a workshop on schizophrenia held in Switzerland. It was a *post-hoc* analysis comparing olanzapine with risperidone, ziprasidone and quetiapine in three separate studies and reported on prevention of relapse. The data for the comparison with risperidone was referenced to Tran *et al* (1997). The poster concluded that, using multiple definitions of response and relapse, olanzapine was better at reducing relapse in patients with schizophrenia than the comparators.

COMPLAINT

Janssen-Cilag noted that as a result of the release of the poster and a subsequent Lilly press release relating to it, an article appeared in Chemist & Druggist, February 2004. The article included claims that patients on Zyprexa apparently relapsed less frequently than those receiving Risperdal. At the end of the article was a statement: 'For more information: Lilly Medical Information Tel [number given]'. Janssen-Cilag telephoned and requested further information but did not specifically request a copy of the poster. In response, a copy of the poster was volunteered by Lilly's medical information department and sent without delay. Janssen-Cilag alleged that, by issuing the poster, Lilly had breached Clauses 2, 9.1 and 22 of the Code.

Janssen-Cilag noted that Lilly had previously been ruled in breach of the Code for making claims of superior efficacy in preventing relapse based on Tran *et al* (Case AUTH/1325/5/02). In that case the Panel

had noted that Tran *et al* had not been designed to measure relapse rates; maintenance of response as defined by two parameters was not the same as prevention of relapse. The Panel concluded that to claim superior relapse prevention for Zyprexa over Risperdal did not accurately reflect the findings of Tran *et al* and was therefore misleading. Lilly had accepted this ruling. Janssen-Cilag took this to mean that Lilly was not permitted to make claims of superior relapse prevention for Zyprexa compared to Risperdal based on the results of Tran *et al*. Janssen-Cilag was therefore surprised to have received the poster from Lilly's medical information department as further information supporting the article in the Chemist & Druggist which claimed superiority for Zyprexa over Risperdal when it had not been specifically requested.

In intercompany correspondence Lilly had stated that '…a request to Lilly Medical Information Department was made for a copy of a poster that was presented at Davos in February 2004. Our medical information department was able to supply the requester with the poster. I am unaware of any situation that might arise that should lead to the refusal to supply such publications of scientific data. Under Clause 1.2, this is not deemed to be promotional, and there has not been a breach of the above ruling'.

Janssen-Cilag noted that it had not specifically requested a copy of the poster; it had requested further information (as stated at the end of the Chemist & Druggist article) and, in response, a copy of the poster was volunteered.

With regard to Clause 1.2 of the Code, replies made in response to a specific request for information were only exempt if they were accurate and not misleading. The conclusions of the poster were clearly misleading and used data previously ruled to be inappropriate to demonstrate comparative rates of relapse between Zyprexa and Risperdal. Additionally, medical information departments were subject to the Code and the requirements to supply information that was not misleading, was balanced and represented an up-to-date evaluation of all the evidence. Hence, even if a medical information department was asked to supply a specific reference, it should not do so if it was misleading unless it pointed out the misleading element to the requester and attempted to provide a balanced view.

Janssen-Cilag alleged that supply and/or use of this poster by Lilly (regardless of whether it was from their medical information department) was failing to comply with a previous undertaking and therefore in breach of Clause 22 of the Code.

By failing to comply with a previous ruling, it was clear that Lilly had not maintained the high standards expected of the pharmaceutical industry. Janssen-Cilag did not know which part of Lilly was responsible for issuing the press release relating to the poster. The fact that Chemist & Druggist reported this event showed that the press release reached the UK, meaning that Lilly in the UK had responsibility for it, even if its international arm actually produced it. Janssen-Cilag stated that the inability of the UK division of Lilly to control the activities of its UK medical information department to prevent such misleading information being actively supplied in breach of previous undertakings meant that it was not maintaining the expected high standards. Indeed Lilly had an obligation to communicate the misleading nature (and the Panel's rulings) of this data to European and global colleagues so that it could not be misleadingly presented in press releases that would be reported in the UK press. If indeed Lilly was responsible directly for the release of this press release in the UK, then manifestly, it was not adhering to its earlier undertaking and would not have been maintaining high standards.

Given the failure of Lilly's medical information department to comply with a previous undertaking, Janssen-Cilag welcomed the Panel's views on whether Clause 2 of the Code had been breached.

RESPONSE

Lilly denied any breach of the Code and submitted that it had fully complied with the undertaking given in Case AUTH/1325/5/02 and would continue to do so. The poster was submitted and written wholly by the parent USA company and contained no authors affiliated with the UK subsidiary. The poster included comparisons between Zyprexa and each of quetiapine, ziprasidone and Risperdal. As was standard practice a press release was issued to medical journalists in the UK regarding this and other posters being presented by the UK affiliate. From a process view it should be noted that following the standard operating procedure (SOP) for approval of press releases in the UK all were deemed to be non-promotional in that they represented information to the media relating to the release of new pertinent information. Following this press release the Chemist & Druggist contacted Lilly advising that the journal was planning an article and to ask permission to include the telephone number of Lilly's medical information department. Permission was granted. On 24 February 2004 a person identifying herself as a hospital pharmacist contacted medical information and stated that she had seen the article. A routine entry was made in the medical information enquiry log that stated the requester 'wants data behind article'. At this stage it was not possible to confirm or deny that what was asked for was a precise statement of 'more information' or if the poster itself had been requested. The person taking the call was unaware of the poster and had no knowledge of its contents. It was agreed that the poster would be sent by fax.

The only information held by Lilly relating to this poster was the poster itself; there were no other materials that could have been sent in place. The medical information department behaved in a routine manner, which was non-promotional and responded to a request for more information regarding the poster by ascertaining the status of the enquirer and mailing them an appropriate item, ie the poster. Clearly the caller did not identify his or herself as a Janssen-Cilag employee and Lilly noted that the poster contained data on three comparative antipsychotics to Zyprexa and not only Risperdal. There was nothing to suggest that the requester specifically asked for 'data behind the article' relating solely to risperidone.

Lilly regarded the sending out of materials from a medical information department in response to an appropriate request as standard practice. It did not seem a credible claim that in response to a request for further information that the sending out of a poster (an action that was most likely agreed with the sender during the call as the item was faxed and thus a fax number would have been given) was an unreasonable or promotional type of activity. Indeed in this case it was the only apparent option in that no other materials were available nor had been generated that would reasonably meet a level of response considered appropriate.

Lilly submitted that the whole argument assumed a semantic nature in that Janssen-Cilag had contended that 'the poster was not specifically requested' without clearly stating what forms of information were clearly asked for and not commenting on what materials were agreed that could indeed be faxed over. Other than the poster Lilly had no other item that would provide any 'information' as requested.

With regard to Clause 1.2 of the Code the response was both accurate and not misleading. An accurate piece of information was delivered (ie the poster itself) in the absence of any other specific data. Should the enquirer have asked for further information relating specifically to relapse rates comparing Zyprexa and Risperdal they would have been advised or sent the appropriate materials. Lilly repeated that the poster contained data on two comparators to Zyprexa other than Risperdal. Specifically the enquirer, according to Lilly's records, did not specifically ask about the Risperdal component to the poster nor of course identify themselves as a Janssen-Cilag employee but only as a hospital pharmacist. In which case it might not be deemed necessary in the absence of any specific questions relating to the Risperdal component of the data to provide additional supporting materials. Lilly therefore submitted that no breach of Clause 22 of the Code had occurred.

Lilly fully complied with the undertaking given regarding Tran *et al* (Case AUTH/1325/5/02) as detailed above. The press release containing new relevant information relating to a number of clinical studies was considered by Lilly to be a non-promotional item in terms of the SOP that covered its approval. It therefore contended that no breach of Clause 9.1 had occurred.

Lilly did not believe that any of its actions had led to a breach of Clause 2 of the Code.

Lilly confirmed that the poster had not been used in any way for promotional materials. The company noted that the poster contained new data comparing Zyprexa to two other antipsychotics in addition to Risperdal. The press release was made on behalf of Lilly by a public relations agency and sent to a number of appropriate medical journals. The article that appeared in the Chemist & Druggist had not been used in any way. This article would presumably have been written by the medical writers from that journal and thus was neither written by nor on behalf of Lilly. Lilly had made every effort to fully comply with the undertaking given in relation to Case AUTH/1325/5/02. Since that undertaking was given all promotional materials had made no reference to the matters referred to in the undertaking.

PANEL RULING

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

The Panel noted that Case AUTH/1325/5/02 concerned a number of items including a leavepiece containing the claim 'Significant reduction in relapse rates compared to risperidone' referenced to Tran *et al*. The Panel had noted that the Tran paper had not referred to relapse rates. The primary objective of the study was to evaluate the effectiveness and safety of olanzapine versus risperidone during double-blind therapy. The maintenance of response as measured by Tran *et al* had only taken into account Positive and Negative Syndrome Scale (PANSS) total score and Clinical Global Impression (CGI) score. In this regard, the Panel noted that in a study which had specifically examined relapse rates in patients with schizophrenia, relapse was defined by any one of 5 parameters (Csernansky *et al*). In the Panel's view Tran *et al* had not been designed to measure relapse rates; maintenance of response as defined by two parameters, was not the same as prevention of relapse. The Panel had considered that the claim did not accurately represent the findings of Tran *et al* and was misleading in that regard. A breach of Clause 7.2 was ruled. This ruling had been accepted by Lilly which had provided the requisite undertaking and assurance.

Turning to the case now before it, Case AUTH/1570/3/04, the Panel noted that olanzapine and risperidone data from Tran *et al* had been used in the poster produced by Lilly USA. The poster concluded that, *inter alia*, olanzapine was better at reducing relapse in patients with schizophrenia than risperidone, ziprasidone or quetiapine using different definitions of response and relapse. The Panel considered that the poster *per se* was not subject to the Code. It had been displayed in an academic forum organised by a third party in Switzerland. Lilly's use of the poster in the UK, however, must comply with the Code.

Lilly UK had issued a press release to medical journals. The press release was entitled 'Zyprexa superior head-to-head to other atypicals in schizophrenia relapse-prevention' followed by 'Additional quality of life data shows Zyprexa benefits vs other atypicals may lead to better patient outcomes over time'. The press release referred to the new data (the poster) which demonstrated that Zyprexa-treated patients experienced significantly longer delays to schizophrenia-relapse in comparison to patients who received other leading atypical antipsychotics. The Panel noted its comments and rulings about the Tran data as detailed above. The press release also stated that Zyprexa-treated patients relapsed significantly less than Risperdal treated patients ($p \leq 0.001$).

With regard to the provision of the poster to Janssen-Cilag in response to the request to Lilly's medical information department, the Panel wondered what else Janssen-Cilag was expecting if not the poster.

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

The Panel noted that the data in the poster relating to the comparison of relapse rates with Zyprexa and Risperdal had been taken from Tran *et al*. Lilly had previously accepted (Case AUTH/1325/5/02) that Tran *et al* was not designed to measure relapse rates. Lilly had issued a press release about the poster.

The Panel considered that the press release and the poster were misleading with regard to the comparative efficacy of Zyprexa and Risperdal to prevent relapse in schizophrenia. The Panel considered that the press release and Lilly's use of the poster meant that the company had not complied with its undertaking. The Panel thus ruled a breach of Clause 22 of the Code. High standards had not been maintained and a breach of Clause 9.1 of the Code was ruled. The Panel also considered that by not complying with an undertaking Lilly had brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel thus ruled a breach of Clause 2 of the Code.

During its consideration of this case the Panel was concerned that the press release referred to the data as new; Tran *et al* was published in 1997. Although the poster reported the results of a new *post-hoc* analysis, the data used was not new. The Panel requested that Lilly be advised of its concerns.

APPEAL BY LILLY

Lilly noted that Case AUTH/1325/5/02 had concerned a number of items including a leavepiece containing the claim 'Significant reduction in relapse rates compared to risperidone', referenced to Tran *et al*, and immediately followed by a graph to illustrate the point. The graph was from Tran *et al* and depicted the cumulative percentage of patients maintaining a response for up to 200 days of treatment. The Panel had noted that Tran *et al* had not referred to relapse rates and that maintenance of response had only taken into account PANSS total score and CGI score. This was considered misleading in that it did not accurately represent the findings of Tran *et al*. The Panel's ruling further stated 'maintenance of response as defined by two parameters was not the same as prevention of relapse'. This ruling was based on a review of Csernansky *et al*.

With regard to PANSS and CGI, Lilly explained that PANSS was a 30 item inventory of general psychopathology used to evaluate the effects of medicinal treatment in schizophrenia. There were 7 items on the positive subscale, 7 on the negative subscale and 16 items on the general psychopathology scale. All items were rated with a score from 1 (absent) to 7 (extreme), giving a range of scores from 30 to 210. CGI assessment reflected the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. The CGI scale was a valid, reliable instrument to evaluate severity and treatment response in schizophrenia. Given its simplicity, brevity and clinical face validity, the scale was appropriate for use in observational studies and routine clinical practice. The scale had a single item, scored from 1 (normal, not ill) to 7 (extremely ill).

Lilly had accepted the Panel's ruling in Case AUTH/1325/5/02 and provided the requisite undertaking and assurance on 15 August 2002.

Lilly noted that during 7-14 February 2004, the Roychowdhury *et al* poster was presented at a major schizophrenia conference in Davos, Switzerland. Roychowdhury *et al* demonstrated that patients with schizophrenia who received Zyprexa experienced significantly longer delays to relapse in comparison to patients who received other atypical antipsychotics.

On 11 February 2004 Lilly issued a press release in respect of the Roychowdhury *et al* poster to medical trade journalists.

On 21 February 2004 an article appeared in Chemist & Druggist regarding the poster. At the end of this article there was a statement – 'For more information: Lilly Medical Information …'. A person, identifying themselves as a hospital pharmacist (who later transpired to be a representative of Janssen-Cilag) contacted Lilly medical information requesting further information regarding the article in Chemist & Druggist and was sent a copy of the poster.

Lilly noted that on 9 March 2004 it had received a letter from Janssen-Cilag alleging that it had failed to comply with its 2002 undertaking and thus breached Clauses 22, 9.1 and 2 for claiming superior relapse prevention based on Tran *et al*.

Lilly submitted that the purpose of the above information was to give the contextual background to the complaint.

Lilly noted that Janssen-Cilag had alleged:-

- That a copy of the Roychowdhury *et al* poster was **volunteered** by Lilly's medical information department and that, with the supply and/or use of this poster, Lilly had failed to comply with a previous undertaking in breach of Clause 22 of the Code.
- That the inability of Lilly to control the activities of its medical information department to prevent misleading information being **actively supplied** in breach of previous undertakings meant that it had not maintained high standards in breach of Clause 9.1 of the Code.

Lilly noted that the Panel had ruled a breach of Clause 22 of the Code. It, however, submitted that Roychowdhury *et al* was different to Tran *et al*. In Tran *et al*, 'Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia

and other psychotic disorders', the primary intent was to evaluate the efficacy and safety of olanzapine versus risperidone in 339 patients over 28 weeks. Although a formal definition of relapse was not included in the publication, a survival analysis was performed to assess 'time maintaining response'. For this analysis, patients were considered to have relapsed if they showed significant symptom exacerbation defined a priori as a 20% or greater worsening in the PANSS total score along with a CGI-S score ≥ to 3 after 8 weeks of therapy.

Roychowdhury *et al* was a *post-hoc* analyses of three studies which compared Zyprexa with quetiapine, Risperdal and ziprasidone respectively in preventing relapse in patients with schizophrenia and related disorders. All the studies were multicentre, double-blind, controlled clinical trials, with patients randomised 1:1 to two active treatments. They all included PANSS total scores as a measure of efficacy and used flexible dosing. This poster was different in many respects to Tran *et al*. It was not a re-presentation of Tran *et al*, it was a new analysis of the patient data set that was used as the basis for Tran *et al* plus the data sets from two other studies. This new analysis was performed by different authors and reached separate conclusions using different statistical methods.

Lilly submitted that the new analysis allowed, unlike Tran *et al*, a clear definition of a responder as either 20% or 30% improvement in PANSS total at 8 weeks. Relapse was defined as 20% or 30% worsening of PANSS total and a CGI-S severity of 3 or more after 8 weeks in the previously clearly defined responder groups. There was no one universally accepted definition of relapse for use in clinical studies hence these definitions of relapse could be regarded as reasonable and clinically meaningful.

Lilly noted the poster contained additional definitions of relapse and response. These had been analysed both by calculating odds ratios and generating new Kaplan-Meier survival curves. These were not performed by the authors of the Tran *et al* paper. These two statistical comparisons reflected major differences as to what was taken into account in the analysis of the data. Odds ratios did not account for time, they compared the proportion of patients who relapsed at any point in the study. Kaplan-Meier survival curves took into account the time the events happened during the study.

Lilly submitted that there was accordingly both additional data and additional analyses in Roychowdhury *et al* that was not present in Tran *et al*. The more comprehensive analyses had been presented in the form of both odds ratios and more detailed survival curves. The conclusions were thus based on these new analyses and allowed clear differentiation of Roychowdhury *et al* from Tran *et al*.

Lilly submitted that in the light of this new information a press release was reasonably made. The title of the press release paraphrased the conclusions stated a number of times by Roychowdhury *et al*. It accurately reported the data and conclusions of their analysis.

Lilly submitted that the complaint was based on Lilly's medical information department supplying a copy of the Roychowdhury *et al* to a Janssen-Cilag employee posing as a hospital pharmacist. The Janssen-Cilag employee had contacted the medical information department to request further information after reading an article in Chemist & Druggist. This article described the poster and concluded 'The findings of the studies, which were sponsored by Eli Lilly, were presented at the 11th Biennial Winter Workshop in Davos, Switzerland'. Although the Janssen-Cilag employee contended that he did not specifically request a copy of the poster and was surprised to be offered it, the fact that the article was specifically about the poster meant that it was reasonable to provide it in response to a request for further information. This was in keeping with the spirit of Clause 1.2 of the Code. The information provided was solely related to the subject matter of the enquiry and the statistical analysis was accurate and the conclusions of the Roychowdhury poster were not misleading because they accurately represented the authors' analysis. This poster was not used promotionally and was only provided upon request.

Lilly submitted that the presentation of the information in the Roychowdhury *et al* poster was scientifically valid, and not misleading. There were still no universally accepted criteria to define relapse in schizophrenia (Lader 1995, Leucht *et al*, 2003). Since the publication of Tran *et al* several papers had been published on the subject of relapse in schizophrenia and there was no consistent definition of what constituted a relapse (Robinson *et al* 1999; Herz *et al* 2000; Csernansky *et al*; Leucht *et al* and Almond *et al* 2004).

Lilly noted that Tran *et al* had used limited criteria to define significant symptom exacerbation as ≥ 20% worsening in PANSS total score and CGI-S ≥ 3. Other recent studies had used different cut-off points to define relapse, as discussed above, making comparisons between studies difficult. Roychowdhury *et al* sought to compare a number of widely used atypical antipsychotic medicines using various commonly accepted definitions of response and relapse. The information included in the poster was not previously available in the public domain. Publication of the poster allowed the reader to make a more direct comparison with subsequent research by Lilly and other pharmaceutical companies.

Lilly submitted that in summary, the Panel's opinion that the Roychowdhury *et al* poster and press release were misleading with regard to the comparative efficacy of Zyprexa and Risperdal to prevent relapse in schizophrenia was based on the previous ruling (AUTH/1325/5/02) that Tran *et al* was not designed to measure relapse rates. As discussed above the poster was a separate piece of work from Tran *et al*. Roychowdhury *et al* did not re-present the Tran data; the authors had reanalysed the patient data set using new methods as described above using many of the various available criteria to describe relapse in schizophrenia. Tran *et al* was cited in Roychowdhury *et al* as this was a prior publication from one of the data sets used for the analysis and the paper described the methodology of the clinical trial. The other prior publications were also referenced. This

was done to make it clear that it was not simply a re-publication of Tran *et al* but a distinct piece of work. Re-analysis in this way was an accepted method of extracting clinically relevant information from the original patient data set. Every clinical trial generated a source of valuable but expensive information. To fully exploit the knowledge hidden in this information, the results should be analysed using a broad range of tools. Lilly stated that it was a widespread practice to perform post hoc analyses of studies and cited examples of publications generated in this way (Wyatt *et al* 1997, Judd *et al* 2003 and Donaldson *et al* 2000).

Lilly noted that the Panel had previously ruled that Tran *et al* described maintenance of response, not relapse prevention. Roychowdhury *et al* described relapse prevention in patients with schizophrenia and the press release quoted this. Schizophrenia was a lifelong disease characterised by periods of relapse and remission and there were no standard criteria to describe these events. Lilly therefore maintained that the criteria used by Roychowdhury *et al* to define relapse were appropriate, measurable, clinically meaningful and robust.

With regard to the Panel's ruling of a breach of Clause 9.1, failure to maintain high standards, Lilly submitted that it not intended to promote the comparative efficacy of Zyprexa and Risperdal to prevent the relapse of schizophrenia based on Tran *et al*. Roychowdhury *et al* was not a re-presentation of Tran *et al*, it was a new analysis of the patient data set that was used as the basis for Tran *et al* plus the data sets from two other studies. As described above, this new analysis was performed by different authors and reached separate conclusions using different statistical methods.

Lilly also noted that the Panel had ruled a breach of Clause 2 of the Code, based on the fact that by not complying with an undertaking, it had brought discredit upon and reduced confidence in the pharmaceutical industry. Lilly did not consider it was in breach of Clauses 22 and 9.1 of the Code and did not, therefore, consider it was in breach of Clause 2.

Lilly noted that a ruling of a breach of Clause 2 was a sign of 'particular censure' which should be reserved for such circumstances. Lilly submitted that the criteria used by Roychowdhury *et al* to define relapse were appropriate, measurable, clinically meaningful and robust, and even if the Appeal Board disagreed with it on this particular point, it believed that it could well have been a reasonable belief in the circumstances. Lilly also considered that the press release and the provision of the poster on request was done in good faith, based on its interpretation of the differences between Roychowdhury *et al* and Tran *et al* and not done in deliberate contravention of the undertaking given in Case AUTH/1325/5/02.

COMMENTS FROM JANSSEN-CILAG

Janssen-Cilag alleged that supply and/or use of Roychowdhury *et al* by Lilly (regardless of whether it was by its medical information department) was failing to comply with a previous undertaking and consequently was in breach of Clause 22 of the Code.

Janssen-Cilag alleged that the inability of Lilly to control the activities of its medical information department to prevent misleading information being actively supplied in breach of previous undertakings meant it was not maintaining the expected high standards and therefore in breach of Clause 9.1 of the Code. Janssen-Cilag stated that when it submitted its complaint it did not know which part of Lilly was responsible for issuing the press release. It was now clear that the UK division issued the press release to medical journalists in the UK and that it gave permission for Chemist & Druggist to include its telephone number at the end of the article.

Janssen-Cilag noted that Lilly had claimed that Roychowdhury *et al* was different to Tran *et al* primarily because the new analysis allowed, unlike Tran *et al*, a clear definition of a responder as either 20 or 30% improvement in PANSS total at 8-weeks. Relapse was defined as 20-30% worsening of PANSS total and a CGI-severity of 3 or more after 8 weeks in the previously clearly defined responder group.

Janssen-Cilag failed to understand how this could be an explanation for the poster and publication being described as different. Both reported on the same set of data (ie data from a study that was designed to evaluate the effectiveness and safety of Zyprexa versus Risperdal, not the relative relapse potential of the two products). In Tran *et al* a survival analysis was performed to estimate time maintaining response (time not exhibiting a significant symptom exacerbation after achieving response criteria at 8 weeks). A significant symptom exacerbation was defined as a 20% or greater worsening in PANSS total score along with a CGI-S score of >3 after 8 weeks of therapy. Only responders ie patients who showed improvement in PANSS total score of at least 20% from baseline at week 8 were included in this analysis.

Janssen-Cilag alleged that it was clear, therefore, that Tran *et al* had provided a clear definition of a responder and that, effectively the same definition which was used to determine maintenance of response in the peer-reviewed publication of this data was being interpreted by Roychowdhury *et al* as relapse. Maintenance of response was not the same as relapse (as ruled in Case AUTH/1325/5/02).

Janssen-Cilag noted that in Case AUTH/1325/5/02, Lilly was ruled in breach of the Code for using this 'maintenance of response' data from Tran *et al* to claim superior relapse prevention potential for Zyprexa compared to Risperdal. Lilly had accepted this ruling. Janssen-Cilag felt strongly that the data in Roychowdhury *et al* was not new – it was merely a re-presentation of the data already in Tran *et al*. Janssen-Cilag alleged that continued use of such data to claim superiority in terms of relapse prevention for Zyprexa over Risperdal must therefore be considered as failure to comply with an undertaking, and the breach of Clause 22 should be upheld. Janssen-Cilag noted that Lilly had stated that this was new data and therefore it was reasonable to issue a press release. The press release was deemed non-promotional and described as containing 'new pertinent information'.

Janssen-Cilag noted that a press release should be factual and not misleading in its content and should

generally relate to new pertinent information. Janssen-Cilag alleged that the contents of the press release were unbalanced, misleading and neither new nor pertinent.

Janssen-Cilag alleged that as described above, issuance of a press release, which allegedly described 'relapse rates', derived from the Tran data should be considered as failing to adhere to the previous undertaking and therefore in breach of Clause 22.

Janssen-Cilag stressed that no employee had posed as a hospital pharmacist in order to obtain information from another company. The employee who contacted Lilly's medical information department was not asked where they were calling from or their profession. If they had been asked, naturally they would have disclosed this information.

Janssen-Cilag noted that before publication of the article in Chemist & Druggist, Lilly agreed to the rider 'For more information: Lilly Medical Information Tel [number supplied]' being placed at the foot of the article. The Janssen-Cilag employee did not request the poster *per se*; they made a request 'for more information' as per the footnote on the article; at this time Lilly was aware that the only additional information available was the poster and that the poster contained information previously ruled in breach of the Code; Lilly must have anticipated that the poster would be sent out on request. To maintain high standards this should have been anticipated; The poster was not a peer reviewed article – all authors were Lilly employees ie all information contained within the poster was generated internally with no external review.

Janssen-Cilag alleged that in order to comply with the spirit of Clause 1.2, any response should not be misleading. The contents and conclusions in the poster were undoubtedly misleading and therefore supplying it through medical information (particularly when it was not directly requested and sufficient explanation of its misleading nature was not given) was subject to the Code and represented a failure to maintain the high standards expected of the pharmaceutical industry and to comply with the previous undertaking.

Janssen-Cilag agreed with Lilly's submission that there was still no universally accepted criteria to define relapse. However, extreme care must be taken especially when addressing a *post-hoc* analysis. Janssen-Cilag alleged that if a study was not specifically designed to address a question it was possible that the definition of relapse used was the one most likely to result in the desired conclusion. Janssen-Cilag noted that Glick and Berg (2002) concluded that 'Using the measures of study discontinuation, relapse and non-compliance, in one trial the atypical antipsychotic olanzapine was superior to haloperidol, while in a second (Tran *et al*) there were no differences between olanzapine and risperidone'. It was therefore possible to exploit the fact that there was no one definitive definition for relapse and *post-hoc* analyses of such should be reviewed appropriately.

Janssen-Cilag alleged that with regard to the comparative relapse prevention potential of Risperdal and Zyprexa, Roychowdhury *et al* was not new data. It was a new representation of the analysis that was actually in the original publication (where it was correctly referred to as maintenance of response). Maintenance of response was not the same as relapse (as ruled in Case AUTH/1325/5/02). The data in itself was misleading, especially given the published data available for Risperdal with regard to relapse prevention, but more importantly it was an analysis of data that had already been ruled unsuitable for making claims of superior relapse prevention potential.

Janssen-Cilag maintained that Lilly's use of the poster (in terms of producing a press release) and the supply of it from medical information was failure to comply with an undertaking and strongly considered that Clause 22 had been breached.

Janssen-Cilag noted that Lilly had stated that it was not its intention to promote the comparative efficacy of Zyprexa and Risperdal to prevent the relapse of schizophrenia based on Tran *et al*. Lilly claimed it was a new analysis of the data set used for Tran *et al*.

Janssen-Cilag failed to accept this as grounds for appeal. As described above this was merely a new representation of old data (with methodological flaws) that was not designed to address relapse. The data it was based upon and the conclusions made were accepted by Lilly to be in breach of the Code in Case AUTH/1325/5/02. It was therefore particularly irresponsible of Lilly to issue a press release when it had already been found in breach of the Code for making a claim of superior relapse prevention based on Tran *et al*.

Furthermore, by issuing a press release there was the implication that this was a new study worthy of public interest. Janssen-Cilag alleged that it was not new data so it was inappropriate for a press release to be issued. Doing so, especially in light of the previous ruling, was indeed failing to maintain the high standards expected of the pharmaceutical industry. Janssen-Cilag therefore alleged that the breach of Clause 9.1 should be upheld.

Janssen-Cilag noted that Lilly had issued a press release and supplied a poster which contained statements previously found in breach of the Code. Janssen-Cilag therefore maintained that Clauses 22 and 9.1 had been breached. In the original complaint, Janssen-Cilag welcomed the Panel's views on whether Clause 2 of the Code had been breached. The Panel considered that by not complying with an undertaking Lilly had brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel thus ruled a breach of Clause 2 of the Code. Janssen-Cilag supported the ruling of the Panel.

APPEAL BOARD RULING

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

The Appeal Board noted the parties' submissions on the debate in the scientific community with regard to

accepted definitions of relapse in schizophrenia. The Appeal Board further noted that the source data which had formed the basis of Tran *et al* had been reanalysed and presented by Roychowdhury *et al*. It was not a reanalysis of the data produced by Tran *et al* but a reanalysis of the data used by that group in its comparison of olanzapine and risperidone. In the Appeal Board's view reanalysis of source data was a valid scientific methodology. Roychowdhury *et al* had applied different definitions than those used by Tran *et al*. Tran *et al* had defined a significant symptom exacerbation as a 20% or greater worsening in the PANSS total score along with a CGI-S score ≥ 3 after 8 weeks' therapy; Roychowdhury *et al* defined relapse as a 20% or 30% worsening on PANSS total score and a CGI-S score of ≥ 3 after 8 weeks in responders. The Appeal Board considered that this new analysis was sufficiently different from Tran *et al* such that use of Roychowdhury *et al* did not represent a breach of the undertaking given in Case AUTH/1325/5/02. No breach of Clause 22 was ruled. Consequently the Appeal Board also ruled no breaches of Clauses 9.1 and 2 of the Code. The appeal was successful.

Complaint received **29 March 2004**

Case completed **17 June 2004**

CASE AUTH/1572/4/04

NOVARTIS v ROCHE

Bondronat journal advertisement

Novartis complained about two journal advertisements, one an abbreviated advertisement, for Bondronat (ibandronate) issued by Roche.

Bondronat (tablets and a concentrate solution for intravenous administration (IV)) was indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. In addition, Bondronat IV was also indicated for the treatment of tumour-induced hypercalcaemia with or without metastases.

Novartis supplied Zometa (zoledronic acid) which had similar indications to Bondronat. Both products belonged to a class of medicines known as bisphosphonates.

Novartis stated that the claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy' which appeared as a heading to the advertisement, referenced to Body *et al* (2003), implied that there was head-to-head data directly comparing the efficacy of Bondronat IV and Bondronat tablets. There had been no head-to-head studies of Bondronat versus any agent other than placebo and the data for both formulations came from three placebo-controlled trials, so only indirect comparisons could be made.

Novartis further stated that since Bondronat tablets were not indicated for tumour-induced hypercalcaemia, it failed to see how the efficacy could be similar to Bondronat IV, and alleged that the claim was misleading and inconsistent with the particulars listed in the summary of product characteristics (SPC). Although the phrase 'For patients with breast cancer and bone metastases' appeared later in the advertisement, this was in much smaller type further down the page and so not obvious to the reader. Novartis alleged that the claim was not in accordance with the marketing authorizations for the two formulations, it was not factually correct, was misleading and could not be substantiated.

The Panel noted that immediately beneath the claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy' appeared an illustration of three skeletons crossing the finishing line in a running race. The Panel considered that the claim implied that a direct comparison of Bondronat IV with Bondronat tablets had concluded that the two formulations had equivalent efficacy. This was not so. The comparable efficacy claim had come from a study (Body *et al*) which had analysed results across three different studies, two comparing oral Bondronat with placebo and one comparing Bondronat IV with placebo. The illustration of one race being run added to the impression that the comparative data was from one study. The Panel considered that the claim was misleading and not capable of substantiation. Breaches of the Code were ruled.

The Panel considered that the advertisement implied that the two formulations had equivalent efficacy in all indications. The advertisement was published in Hospital Doctor and would therefore be seen by doctors who would treat hypercalcaemia of malignancy and patients with breast cancer and bone metastases. In the Panel's view some doctors might think that Bondronat was the first third generation bisphosphonate which could be given orally in the treatment of hypercalcaemia of malignancy which was not so. Bondronat tablets were not so licensed. The Panel did not consider that the impression given by the headline that oral Bondronat could be given to the same patients as Bondronat IV was negated by the inclusion of the claim beneath the illustration 'For patients with breast cancer and bone metastases'. The headline claim needed to be read in conjunction with the qualifying text in order for its clinical implications to be understood. The Panel considered that the claim on its own was inconsistent with the particulars listed in the SPC for Bondronat tablets and a breach of the Code was ruled.

Upon appeal by Roche, the Appeal Board considered that the claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy' was a strong, unequivocal statement. The claim was referenced to Body *et al* which had taken

the results from three different placebo controlled studies using two different formulations. In none of the studies were IV and oral Bondronat directly compared. The study authors had concluded, *inter alia*, that their results suggested that both IV and oral Bondronat were equally effective. The Appeal Board noted that such caution was not reflected in the claim at issue. The Appeal Board considered that the claim gave the impression that a direct clinical comparison of IV and oral Bondronat had proven that the two were equally effective which was not so. The Appeal Board upheld the Panel's rulings of breaches of the Code.

The Appeal Board noted that Bondronat tablets, unlike the IV formulation, could not be used to treat hypercalcaemia of malignancy. The claim at issue referred to equivalent IV and oral efficacy. The Appeal Board noted, however, that the advertisement had appeared in Hospital Doctor; it was thus aimed at a specialist audience which in the Appeal Board's view would not consider oral therapy for hypercalcaemia of malignancy. The Appeal Board also noted that the main text of the advertisement began 'For patients with breast cancer and bone metastases …'. Given the intended audience and the main text of the advertisement, the Appeal Board did not consider that the claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy' was inconsistent with the particulars listed in the oral Bondronat SPC as alleged. No breach of the Code was ruled.

Novartis noted the claim '… renal safety profile comparable to placebo in trials' and stated that bisphosphonates were associated with nephrotoxicity. This major organ toxicity had been recognised within the licence for both formulations of Bondronat. Both SPCs stated:

'Clinical studies have not shown any evidence of deterioration in renal function with long term Bondronat therapy. Nevertheless, according to clinical assessment of the individual patient, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with Bondronat.'

The SPC for oral Bondronat further stated that for adverse drug reactions occurring at a frequency of <1%, azotaemia (uraemia) occurred more frequently with Bondronat tablets than with placebo. The Bondronat IV SPC stated that creatinine increase occurred in 2% of Bondronat patients compared with 0.6% of placebo patients. Novartis stated that these percentages might appear small but the potential clinical sequelae of renal impairment and renal failure could result in significant morbidity and mortality. Novartis alleged that the claim implied that unlike other bisphosphonates renal toxicity was not a potential concern for Bondronat.

The Panel noted that the Bondronat SPCs both stated: 'Clinical studies have not shown any evidence of deterioration in renal function with long term Bondronat therapy. Nevertheless according to clinical assessment of the individual patient it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with Bondronat'.

The Panel accepted that there might be differences between the Bondronat and Zometa SPCs in relation to monitoring renal function as submitted by Roche. However the claim at issue implied that the risk of renal side effects was so small that clinicians need not consider them and this was not so given the SPC recommendations for renal monitoring and the inclusion of uraemia as an uncommon adverse event for oral Bondronat. The Panel considered the claim '… renal safety profile comparable to placebo in clinical trials' was a misleading comparison and thus ruled a breach of the Code.

Upon appeal by Roche, the Appeal Board noted that the SPCs for both IV and oral Bondronat stated 'Clinical studies have not shown any evidence of deterioration in renal function with long term Bondronat therapy' and went on to state 'Nevertheless, according to clinical assessment of the individual patient, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with Bondronat'. The Appeal Board considered that notwithstanding this second statement, which in its view was a class warning, the renal profile of Bondronat was different to that of other bisphosphonates. The Appeal Board thus considered that the claim '… renal safety profile comparable to placebo in trials' was not unreasonable. It was sufficiently clear that the renal safety profile data was derived from clinical trials. The Appeal Board ruled no breach of the Code.

Novartis noted the claim 'So with equivalent efficacy and a small once-daily tablet, compared to IV, Oral Bondronat offers all the convenience and flexibility you could want from today's bisphosphonate therapy' and stated that the SPC for Bondronat tablets required that the tablets be taken once daily, after an overnight fast (at least 6 hours) and before the first food or drink of the day. Fasting should be continued for at least 30 minutes after taking the tablet and patients should remain upright for 60 minutes. In addition, patients were advised not to chew or suck the tablets.

Novartis noted that the SPC of another oral bisphosphonate, clodronate (Bonefos, Boehringer Ingelheim) tablets, stated that the tablets could be taken as a single dose, at least 1 hour before or 1 hour after food. Novartis alleged that the all encompassing claim of convenience and flexibility for oral Bondronat was not factually correct, misleading, exaggerated and not capable of substantiation.

The Panel noted that the claim was a comparison of oral and IV Bondronat. In that regard the Panel considered that oral therapy would usually be more convenient than IV treatment. The claim, however, also referred to 'today's bisphosphonate therapy' and in that regard the Panel noted that there were three oral bisphosphonates indicated for the treatment of patients with breast cancer and bone metastases; Bonefos, Loron and Bondronat. Bonefos and Loron were to be taken in a single dose or two

divided doses each day, at least one hour before and one hour after food. Bondronat tablets were to be taken after an overnight fast of at least six hours and at least 30 minutes before the first food or drink of the day. The Panel considered there was thus less flexibility with regard to the time of day that a patient could take Bondronat compared with the other oral bisphosphonates. The Panel noted Roche's submission about the small tablet size but noted that there was no data to show whether patients found these more or less convenient than other bisphosphonate tablets. The Panel thus considered that in the context of 'today's bisphosphonate therapy' oral Bondronat was less convenient and flexible in terms of timing of dosage than other oral bisphosphonates. The Panel thus ruled breaches of the Code.

Upon appeal by Roche, the Appeal Board noted that the claim in question appeared thus in the advertisement:

> **'So with equivalent efficacy and a small once-daily tablet, compared to IV, Oral Bondronat offers all the convenience and flexibility you could want from today's bisphosphonate therapy'**

The use of a capital O for Oral Bondronat gave the impression that Oral Bondronat was the start of the claim and it was this second half of the sentence which Novartis had referred to in its complaint and response to Roche's appeal.

The Appeal Board considered that the claim was more than a comparison between IV and oral; the reference to 'today's bisphosphonate therapy' turned it into a comparison of oral Bondronat with all other bisphosphonates. The Appeal Board thus considered that by stating oral Bondronat offered <u>all</u> (emphasis added) the convenience and flexibility a prescriber could want the claim was misleading, not capable of substantiation and exaggerated as alleged. The Appeal Board upheld the Panel's rulings of breaches of the Code.

Novartis alleged that the claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy' which appeared beneath the heading 'New in metastatic bone disease due to breast cancer' in the abbreviated advertisement was in breach of the Code.

The Panel considered that its rulings above of breaches of the Code regarding the comparison of oral and IV Bondronat applied here to the abbreviated advertisement and ruled accordingly. This was confirmed upon appeal.

The Panel considered that unlike the advertisement considered above, the abbreviated advertisement made it clear from the outset that the indication was metastatic bone disease due to breast cancer as this appeared as a heading and would be read before the claim at issue. The Panel thus did not consider that the impression was given that oral Bondronat and Bondronat IV had equivalent indications. No breach of the Code was ruled.

Novartis Pharmaceuticals UK Ltd complained about the promotion of Bondronat (ibandronate) by Roche Products Limited. The material at issue was an advertisement published in Hospital Doctor, 4 March 2004 (ref J116053), and an abbreviated advertisement published in MIMS March 2004 (ref J116083).

Bondronat was available as film coated tablets and as a concentrate solution for intravenous administration (IV). Both products were indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. In addition, Bondronat IV was also indicated for the treatment of tumour-induced hypercalcaemia with or without metastases.

Novartis supplied Zometa (zoledronic acid) which had similar indications to Bondronat. Both products belonged to a class of medicines known as bisphosphonates.

A Hospital Doctor advertisement

1 Claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy'

The claim appeared as a heading to the A3 advertisement and was referenced to Body *et al* (2003).

COMPLAINT

Novartis stated that the claim gave the impression that there was head-to-head data directly comparing the efficacy of Bondronat IV and Bondronat tablets. There had been no head-to-head studies of Bondronat versus any agent other than placebo and the data for both formulations of Bondronat came from three placebo-controlled trials. There was no head-to-head trial data comparing the two formulations of Bondronat, so only indirect comparisons could be made.

Novartis stated that since Bondronat tablets were not indicated for tumour-induced hypercalcaemia, it failed to see how the efficacy could be similar to Bondronat IV, and alleged that the claim was misleading and inconsistent with the particulars listed in the summary of product characteristics (SPC).

Novartis stated that although the phrase 'For patients with breast cancer and bone metastases' appeared later in the advertisement, this was in significantly smaller font further down the page and hence was not obvious to the reader.

Novartis alleged that the claim was not in accordance with the marketing authorizations for the two formulations, it was not factually correct, was misleading and could not be substantiated. Breaches of Clauses 3.2, 7.2, 7.3 and 7.4 of the Code were alleged.

RESPONSE

Roche submitted that the claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy' was factually correct, clear and could be substantiated.

Three pivotal double-blind, placebo-controlled, phase III studies (two using oral Bondronat and one using

IV Bondronat) were the basis for the SPCs. These trials used identical inclusion and exclusion criteria. The SPCs for the IV and oral formulations with respect to metastatic bone disease, the subject of the advertisement, had identical indications. Section 5.1 of the Bondronat IV SPC described a 40% reduction in the primary endpoint of skeletal related events over the placebo control group (p=0.003). The oral SPC described a 38% reduction in the primary endpoint of skeletal related events over the placebo control group (p=0.003). Bone pain was a common and distressing symptom of metastatic bone disease. Bone pain was significantly improved compared to placebo as stated in the IV SPC (p<0.001) and the oral SPC (p=0.001). A significant improvement was also seen for both formulations for quality of life (IV p=0.004, oral p=0.032). A reader of the IV and oral SPCs for Bondronat could not differentiate the advantages or disadvantages of either formulation based on efficacy alone. They were equally effective. That was not to imply that both formulations were equally suitable for a given patient. For example, a patient might be unable to swallow and IV was preferred. Such decisions were, of course, implicit in the management of the patient and this was where Bondronat could provide such flexibility unhampered by compromising efficacy between formulations.

Body *et al* described a multivariate Poisson regression analysis of new bone events in patients from the three pivotal trials. This analysis showed significant and comparable risk reductions for both formulations compared to placebo including significant pain score reduction from baseline. The authors also found a consistent and statistically significant effect of the 50mg oral dose which was comparable to the effect of 6mg intravenous dose of ibandronate.

Roche stated that in suggesting that the claim misled the reader about hypercalcaemia of malignancy, Novartis chose to take the whole advertisement out of context and failed to recognise the expertise of the prescriber who treated hypercalcaemia of malignancy and metastatic bone disease. This entire advertisement related to metastatic bone disease. This was obvious as it was clearly cited in the next line 'For patients with breast cancer and bone metastases …'. Nowhere in the advertisement (including the prescribing information) was any other indication mentioned. Hypercalcaemia of malignancy often presented as a medical emergency and urgent IV rehydration and IV bisphosphonate therapy was warranted. The expert prescribers who used bisphosphonates in hypercalcaemia of malignancy would know this and that oral medicines were not used to reduce serum calcium levels in the required 24-48 hour period.

PANEL RULING

The Panel noted that immediately beneath the claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy' appeared an illustration of three skeletons crossing the finishing line in a running race.

The Panel considered that the claim at issue implied that a direct comparison of Bondronat IV with Bondronat tablets had concluded that the two formulations had equivalent efficacy. This was not so. The reference, Body *et al*, examined three studies, two comparing oral Bondronat with placebo and one comparing Bondronat IV with placebo. Body *et al* had undertaken a multivariate Poisson regression analysis to determine whether IV and oral Bondronat were similar in the reduction of the risk for developing skeletal events and stated that the results suggested that both formulations were equally effective. The illustration of one race being run added to the impression that the comparative data was from one study. The Panel considered that the claim was misleading and not capable of substantiation. Breaches of Clauses 7.2, 7.3 and 7.4 of the Code were ruled.

The Panel considered that the advertisement implied that the two formulations had equivalent efficacy in all indications. The advertisement was published in Hospital Doctor and would therefore be seen by doctors who would treat hypercalcaemia of malignancy and patients with breast cancer and bone metastases. In the Panel's view some doctors might think that Bondronat was the first third generation bisphosphonate which could be given orally in the treatment of hypercalcaemia of malignancy which was not so. Bondronat tablets were not licensed for the treatment of tumour-induced hypercalcaemia. The Panel did not consider that the impression given by the headline that oral Bondronat could be given to the same patients as Bondronat IV was negated by the inclusion of the claim beneath the illustration 'For patients with breast cancer and bone metastases'. The supplementary information to Clause 7 of the Code stated that it should be borne in mind that claims in promotional material must be capable of standing alone as regards efficacy etc. In general claims should not be qualified by the use of footnotes and the like. The headline claim needed to be read in conjunction with the qualifying text in order for its clinical implications to be understood. The Panel considered that the claim on its own was inconsistent with the particulars listed in the SPC for Bondronat tablets and a breach of Clause 3.2 of the Code was ruled.

APPEAL BY ROCHE

Roche submitted that the claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy' was made in the context of the whole advertisement. There was no mention of hypercalcaemia of malignancy. Hypercalcaemia of malignancy was a medical emergency treated by experienced clinicians none of whom would consider anything other than IV therapy. There was no suggestion that oral Bondronat could be used for hypercalcaemia of malignancy and the claim should not be considered in breach of Clause 3.2.

Roche noted that the word 'equivalent' was defined in the Concise Oxford Dictionary as, *inter alia*, 'equal in value' and 'having the same result'. It did not imply a direct head-to-head comparison.

Roche noted that the SPC for oral Bondronat cited a 38% reduction in the risk of skeletal related events compared with placebo – this was clinically

equivalent to the figure of 40% cited in the SPC for IV Bondronat. This claim was, therefore, not misleading, was substantiated by the SPCs, and was not in breach of Clauses 7.2, 7.3, and 7.4.

Roche submitted that the image of three skeletons running with one winning related to the advantages of a third generation bisphosphonate and a reader would have to be very well versed in the details of the study programme to draw the false conclusion that the skeletons represented the three pivotal trials.

Roche submitted that with regard to the Panel's comment about differences in the individual components of the primary endpoints between IV and oral formulations, the studies were not powered to determine statistically significant differences at the level of individual components. This was reflected in the SPCs of Bondronat and other bisphosphonates which were licensed to reduce skeletal related events (made up of several components).

Roche submitted that the primary endpoint of the trials was the overall reduction in skeletal morbidity not the individual components. In addition, in each trial very strict precautions were taken not to count multiple events occurring in the 12 week evaluation periods as these could be related – so that multiple events would only be recorded as one event. With such strict criteria for analysing events, it was clearly not relevant to expect significant differences in any one particular event. However, both in the IV and oral studies, the reduction in the skeletal morbidity period rates was driven by a statistically significant decrease in the need for radiotherapy. Statistically significant differences or trends seen with fractures and surgery were identified despite the low numbers of such events and the trends were all in the clinically appropriate direction. The overall efficacy profile of IV and oral Bondronat was the same.

COMMENTS FROM NOVARTIS

Novartis agreed with the Panel's ruling that the claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy' implied a direct comparison of Bondronat IV with Bondronat tablets which was not the case.

Novartis alleged that Roche's assertion that there was no mention of hypercalcaemia of malignancy did not abrogate the fact that IV Bondronat was licensed for this indication while oral Bondronat was not and therefore the two formulations could not be therapeutically equivalent. In addition, Roche's statement that clinicians would not consider anything other than IV therapy to treat hypercalcaemia of malignancy was spurious since its own oral bisphosphonate, Loron 520 was indicated for 'The management of osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with carcinoma of the breast or multiple myeloma' and a competitor oral bisphosphonate, Bonefos, was indicated for 'The management of osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with carcinoma of the breast or multiple myeloma'. In certain malignancies at least, clinicians therefore had the option to use oral therapy for the management of hypercalcaemia, but this was not true of oral Bondronat which was not licensed in this indication.

Novartis noted that Roche stated that the dictionary definition of 'equivalent' meant 'equal in value' and 'having the same result' and this was clearly not the case for the two formulations of Bondronat since the licensed indications were different.

Novartis considered that Roche's explanation that the three skeletons running represented a third generation bisphosphonate was obscure in the extreme.

APPEAL BOARD RULING

The Appeal Board considered that the claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy' was a strong, unequivocal statement. The claim was referenced to Body *et al* which had taken the results from three different placebo controlled studies using two different formulations. In none of the studies were IV and oral Bondronat directly compared. The study authors had concluded, *inter alia*, that their results suggested that both IV and oral Bondronat were equally effective. The Appeal Board noted that such caution was not reflected in the claim at issue. The Appeal Board considered that the claim gave the impression that a direct clinical comparison of IV and oral Bondronat had proven that the two were equally effective which was not so. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.4 of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted that Bondronat tablets, unlike the IV formulation, could not be used to treat hypercalcaemia of malignancy. The claim at issue referred to equivalent IV and oral efficacy. The Appeal Board noted, however, that the advertisement had appeared in Hospital Doctor; it was thus aimed at a specialist audience which in the Appeal Board's view would not consider oral therapy for hypercalcaemia of malignancy. The Appeal Board also noted that the main text of the advertisement began 'For patients with breast cancer and bone metastases …'. Given the intended audience and the main text of the advertisement, the Appeal Board did not consider that the claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy' was inconsistent with the particulars listed in the oral Bondronat SPC as alleged. No breach of Clause 3.2 was ruled. The appeal on this point was successful.

2 Claim '… renal safety profile comparable to placebo in trials'

COMPLAINT

Novartis stated that bisphosphonates were associated with nephrotoxicity. This major organ toxicity had been recognised within the licence for both formulations of Bondronat. The SPCs for both Bondronat IV and Bondronat tablets stated the following in the special warnings section:

'Clinical studies have not shown any evidence of deterioration in renal function with long term Bondronat therapy. Nevertheless, according to

clinical assessment of the individual patient, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with Bondronat.'

The SPC for Bondronat tablets further stated that for adverse drug reactions occurring at a frequency of <1%, azotaemia (uraemia) occurred more frequently with Bondronat tablets than with placebo. The SPC for Bondronat IV stated that creatinine increase occurred in 2% of Bondronat patients compared with 0.6% of placebo patients.

Novartis stated that these percentages might appear small but the potential clinical sequelae of renal impairment and renal failure could result in significant morbidity and mortality.

As the claim was specific to the renal safety profile of Bondronat and not to all the adverse events with a comparable frequency to placebo in the trials, it gave the distinct impression that unlike other bisphosphonates renal toxicity was not a potential concern for Bondronat. Novartis alleged that the claim was misleading in breach of Clause 7.3.

RESPONSE

Roche explained that serious concerns over renal safety were emerging with Zometa and were probably the basis for this component of Novartis' complaint, where Bondronat had a competitive advantage.

Roche noted Novartis' allegation that it was misleading to give the distinct impression that unlike other bisphosphonates renal toxicity was not a potential concern for Bondronat. Toxicity of any kind was a 'potential concern' for any medicine but this was not what was claimed. The true impression that was intended was that renal toxicity was not of special clinical concern with Bondronat. This was borne out by the following facts.

Roche agreed that the Bondronat SPC stated that 'Clinical studies have not shown any evidence of deterioration in renal function with long term Bondronat therapy'. No other bisphosphonate could make that claim from its SPC. All patients with metastatic bone disease should be monitored for renal function with a bisphosphonate, but this need only be done 'according to clinical assessment of the individual patient' with Bondronat. The Committee on Proprietary Medicinal Products approved Bondronat after Zometa yet did not find it necessary to stipulate the need to monitor renal function before every dose of Bondronat (unlike Zometa). Uraemia was an uncommon (<1%) finding in trials with oral Bondronat. Only three patients on Bondronat IV compared with one on placebo had an increased serum creatinine (which was not a good indicator of renal function – creatinine clearance was preferred). Indeed, there were many reasons for changes to creatinine levels which were not due to renal deterioration. Variations in levels occurred frequently in healthy individuals after protein meals and/or exercise. The SPC merely reflected changes in creatinine which were incidental findings, and which were not incompatible with the statement that no renal deterioration was seen.

Roche noted Novartis' statement that these percentages might appear small but potential clinical sequelae of renal impairment and renal failure could result in significant morbidity and mortality. This was without substantiation for Bondronat. For the IV pivotal study 'There was no evidence of renal toxicity associated with ibandronate treatment: the incidence of renal adverse events was low and did not differ between placebo and ibandronate groups'. For the oral pivotal studies, 'The incidence of renal [adverse events] was comparable between ibandronate (5.2%) and placebo (4.7%), and there were no reports of serious [adverse events] (renal failure) in the active treatment group'.

No other bisphosphonate had four-year follow on renal safety data to establish no renal toxicity concerns over long term therapy. According to the SPCs, both the oral and IV Bondronat formulations could be used with a dose adjustment in severe renal failure (creatinine clearance less than 30ml/min), unlike Zometa which was contraindicated. There was no caution about Bondronat with nephrotoxic agents (unlike Zometa). Indeed, in over 500,000 patient exposures in Europe since 1996, and unlike any other IV bisphosphonate, Bondronat IV had had no publications raising concerns over renal toxicity.

PANEL RULING

The Panel noted that the SPCs for Bondronat IV and oral Bondronat both stated: 'Clinical studies have not shown any evidence of deterioration in renal function with long term Bondronat therapy. Nevertheless according to clinical assessment of the individual patient it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with Bondronat'.

The Panel accepted that there might be differences between the SPCs in relation to monitoring renal function as submitted by Roche. However the Panel considered that the claim at issue implied that the risk of renal side effects was so small that clinicians need not consider them and this was not so given the SPC recommendations for renal monitoring and the inclusion of uraemia as an uncommon adverse event for oral Bondronat.

The Panel considered the claim '… renal safety profile comparable to placebo in clinical trials' was a misleading comparison and thus ruled a breach of Clause 7.3 of the Code.

APPEAL BY ROCHE

Roche submitted that the claim '… renal safety profile comparable to placebo in trials' simply stated a fact, given the results of the placebo comparator in controlled phase III trials, it was not a misleading comparison and was not a breach of Clause 7.3. This was supported by the SPC statements that 'Clinical studies have not shown any evidence of deterioration in renal function with long term Bondronat therapy'.

Roche noted that uraemia had occurred in one 92 year old woman with ischaemic heart disease, peripheral vascular disease, and hypothyroidism whilst taking oral Bondronat in one of the two pivotal trials. This

was a chance finding, given that the oral formulation was unlikely to achieve the peak plasma concentration required to exceed the renal toxicity threshold (≥ 1000ng/ml).

COMMENTS FROM NOVARTIS

Novartis agreed with the Panel's ruling that the claim '… renal safety profile comparable to placebo in trials' was misleading given the SPC recommendations and inclusion of renal adverse effects in Section 4.8.

Novartis noted that the whole sentence containing the claim read: 'Both IV and new ORAL Bondronat are equally effective in reducing risk of skeletal events and reducing bone pain – with a renal safety profile comparable to placebo in trials'.

Novartis noted that although this claim clearly referred to both formulations of Bondronat, Roche had chosen only to comment on the oral formulation in its appeal.

Novartis also noted that the SPCs for oral and IV Bondronat listed, *inter alia*, the frequency of those renal adverse events which had occurred more frequently with Bondronat than with placebo. The relevant adverse events listed in the oral Bondronat SPC was azotaemia (uraemia) (< 1%) and for IV it was increased creatinine (0.6% placebo, n=157; 2% Bondronat n=152).

Thus both SPCs were unequivocal in stating that recognised measures of renal dysfunction occurred more frequently in Bondronat-treated patients than placebo-treated patients and to claim that the renal safety profile of either formulation was comparable to placebo was not only misleading but potentially threatened patient safety.

APPEAL BOARD RULING

The Appeal Board noted that the SPCs for both IV and oral Bondronat stated 'Clinical studies have not shown any evidence of deterioration in renal function with long term Bondronat therapy.' and went on to state 'Nevertheless, according to clinical assessment of the individual patient, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with Bondronat'. The Appeal Board considered that notwithstanding this second statement, which in its view was a class warning, the renal profile of Bondronat was different to that of other bisphosphonates. The Appeal Board thus considered that the claim '… renal safety profile comparable to placebo in trials' was not unreasonable. It was sufficiently clear that the renal safety profile data was derived from clinical trials. The Appeal Board ruled no breach of Clause 7.3 of the Code. The appeal on this point was successful.

3 Claim 'So with equivalent efficacy and a small once-daily tablet, compared to IV, Oral Bondronat offers all the convenience and flexibility you could want from today's bisphosphonate therapy'

COMPLAINT

Novartis stated that the SPC for Bondronat tablets required that the tablets be taken once daily, after an overnight fast (at least 6 hours) and before the first food or drink of the day. Fasting should be continued for at least 30 minutes after taking the tablet and patients should remain upright for 60 minutes after taking the tablet. In addition, patients were advised not to chew or suck the tablets.

Novartis noted that the SPC of another oral bisphosphonate, clodronate (Bonefos, Boehringer Ingelheim Ltd) tablets, stated that the tablets could be taken as a single dose, at least 1 hour before or 1 hour after food.

Novartis alleged that this all-encompassing claim of convenience and flexibility for oral Bondronat was not factually correct, misleading, exaggerated and not capable of substantiation in breach of Clauses 7.2, 7.3, 7.4 and 7.10 of the Code.

RESPONSE

Roche stated that expert prescribers knew of the problems of previous oral bisphosphonates. This related to clodronate in the UK. It was common knowledge that the size of the clodronate tablet caused problems in swallowing and, together with gastrointestinal (GI) intolerance, the dose of clodronate often had to be fractionated. This required multiple fasting periods throughout the day to allow for absorption. This was complicated for the elderly/confused and disrupted normal living patterns.

In an abstract presented at a recent international bisphosphonate workshop, and with similar data presented in Novartis' own satellite symposium, it was shown that GI toxicity could cause early study discontinuation, with reports of 11-47% of patients reporting upper GI adverse events. These data did not include oral Bondronat. In a long term study of 1,079 patients, GI disorders were significantly more common with clodronate (66%) than placebo (56.2%). One might speculate the high placebo level reflected the size of the tablet required to match the active. Diarrhoea was also significantly more common for clodronate (15.1%) than placebo (6.8%). Complicated regimes and compliance were cited as problems.

Oral Bondronat was small (the size of a 'Tic Tac' mint). On waking (an overnight fast of at least 6 hours) one tablet was taken each day with a tumbler of water and the patient might only take water for the next half hour. This was a simple regime. Non-compliance had not featured in the pivotal studies. The SPC cited levels of GI intolerance (dyspepsia, nausea, abdominal pain and oesophagitis) similar to placebo and low and they were classified as mild.

In relation to the claim 'Oral Bondronat offers all the convenience and flexibility you could want from today's bisphosphonate therapy', Roche could do no better than cite the comment made in the published paper: '… oral ibandronate could offer treatment flexibility for physicians and convenience for patients. Oral ibandronate might be prescribed alongside other

oral agents (particularly hormone treatment) for at-home dosing (eg when hospital care was not being received). Patients would no longer have to spend time travelling to and from the hospital solely for bisphosphonate infusion, allowing them to maintain their lifestyle without disruption. The dosing regimen of oral Bondronat was convenient for patients. Adequate adherence was important in real-life situations, where dosing instructions were not closely monitored, unlike clinical trials'.

PANEL RULING

The Panel noted that the claim was a comparison of oral and IV Bondronat. In that regard the Panel considered that oral therapy would usually be more convenient than IV treatment. The claim, however, also referred to 'today's bisphosphonate therapy' and in that regard the Panel noted that there were three oral bisphosphonates indicated for the treatment of patients with breast cancer and bone metastases: Bonefos, Loron and Bondronat. Bonefos and Loron were to be taken in a single dose or two divided doses each day, at least one hour before and one hour after food. Bondronat tablets were to be taken after an overnight fast of at least six hours and at least 30 minutes before the first food or drink of the day. The Panel considered there was thus less flexibility with regard to the time of day that a patient could take Bondronat compared with the other oral bisphosphonates. If a patient forgot to take Bondronat first thing in the morning, before breakfast, it would be difficult to take it at any other time of day given the need to fast for at least six hours beforehand and 30 minutes after. Patients who forgot to take either Bonefos or Loron could take it later in the day as long as there was a period of at least two hours where they did not eat; to take Bondronat later in the day required a period of at least $6^1/_2$ hours of no food. The Panel noted Roche's submission about the small tablet size but noted that there was no data to show whether patients found these more or less convenient than other bisphosphonate tablets. The Panel thus considered that in the context of 'today's bisphosphonate therapy' oral Bondronat was less convenient and flexible in terms of timing of dosage than other oral bisphosphonates. The Panel thus ruled breaches of Clauses 7.2, 7.3, 7.4 and 7.10 of the Code.

APPEAL BY ROCHE

Roche submitted that to consider a small, once-a-day tablet less convenient than the larger clodronate tablets, which often required fractionated dosing due to compliance and tolerability problems, did not relate to clinical experience or feedback from prescribers. Non-compliance had not been reported in the pivotal trials. The issue of 'flexibility' related to the choice of an IV or oral formulation with equivalent efficacy and safety profiles.

Roche submitted that with respect to other oral bisphosphonates, most patients would not choose to have a midday fast. Due to the nature of the condition and the pharmacokinetics of oral Bondronat, it was unlikely that a patient would suffer harm from missing one tablet that day. The Panel's point about a patient forgetting to take tablets related to compliance and was not part of the claim.

Roche noted that there were two brands of oral clodronate available in the UK. Each had a different tablet size and dosage recommendations. Loron was a 520mg tablet whilst Bonefos was available as a 800mg tablet and a 400mg gelatin capsule. Unlike Bondronat, the number of tablets required was more for clodronate, the dose might need to be divided or doubled, and clodronate was contraindicated in severe renal failure (depriving patients of the continued oral clodronate cover for their metastatic bone disease). There was only one dose for Bondronat (which was modified for those with severe renal failure).

Roche did not consider there had been a breach of Clauses 7.2, 7.3, 7.4, and 7.10.

COMMENTS FROM NOVARTIS

Novartis agreed with the Panel's ruling that in the context of today's bisphosphonate therapy, which included three oral bisphosphonates indicated for the treatment of patients with breast cancer and bone metastases, oral Bondronat was less flexible in terms of timing of dosage than other oral bisphosphonates.

The claim made no reference to compliance and Novartis stated that the comments to this effect in Roche's appeal were irrelevant. In addition, the statement that 'Due to the nature of the condition and the pharmacokinetics of oral Bondronat, it was unlikely that a patient would suffer harm from missing one tablet that day' was entirely spurious and outside the terms of the marketing authorization for Bondronat tablets.

Novartis noted that Roche had described the different brands of oral bisphosphonate on the market but failed to take account of the fact that the marketing authorizations for all of them, stated that the daily dose might be taken at one time after a one hour fast; oral Bondronat had to be taken after a six hour fast.

APPEAL BOARD RULING

The Appeal Board noted that the claim in question appeared thus in the advertisement:

> 'So with equivalent efficacy and a small once-daily tablet, compared to IV, Oral Bondronat offers all the **convenience and flexibility** you could want from today's bisphosphonate therapy'

The use of a capital O for Oral Bondronat gave the impression that Oral Bondronat was the start of the claim and it was this second half of the sentence which Novartis had referred to in its complaint and response to Roche's appeal.

The Appeal Board considered that the claim was more than a comparison between IV and oral. The reference to 'today's bisphosphonate therapy' turned the claim into a comparison of oral Bondronat with all other bisphosphonates.

The Appeal Board thus considered that by stating oral Bondronat offered **all** (emphasis added) the

convenience and flexibility a prescriber could want the claim was misleading, not capable of substantiation and exaggerated as alleged. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.3, 7.4 and 7.10 of the Code. The appeal on this point was unsuccessful.

B MIMS abbreviated advertisement

Claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy'

This claim appeared beneath the heading 'New in metastatic bone disease due to breast cancer'.

COMPLAINT

Novartis alleged that the claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy' was in breach of Clauses 3.2, 7.2, 7.3 and 7.4 of the Code as alleged in point A1 above.

RESPONSE

Roche noted that the claim was prefixed by the heading 'New in metastatic bone disease due to breast cancer'. Novartis had taken the claim out of context. The abbreviated advertisement, as with the advertisement at issue in point A1, clearly and solely related to metastatic bone disease.

PANEL RULING

The Panel considered that its rulings of breaches of Clauses 7.2, 7.3 and 7.4 of the Code in point A1 regarding the comparison of oral and IV Bondronat applied here to the abbreviated advertisement and ruled accordingly.

The Panel considered that unlike the advertisement considered at point A above, the abbreviated advertisement made it clear from the outset that the indication was metastatic bone disease due to breast cancer as this appeared as a heading and would be read before the claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy'. The Panel thus did not consider that the impression was given that oral Bondronat and Bondronat IV had equivalent indications. No breach of Clause 3.2 was ruled. This ruling was not appealed.

APPEAL BY ROCHE

Roche did not specifically appeal the Panel's rulings of breaches of the Code but its appeal at point A1 above was taken to apply here.

COMMENTS FROM NOVARTIS

Novartis made no further comment.

APPEAL BOARD RULING

The Appeal Board considered that its comments at point A1 above regarding the implied direct clinical comparison of oral and IV Bondronat applied here. The Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.4 of the Code were upheld. The appeal on this point was unsuccessful.

Complaint received **2 April 2004**

Case completed **2 August 2004**

CASE AUTH/1574/4/04

PFIZER v ASTRAZENECA

Promotion of Crestor

Pfizer complained about a leavepiece and a journal advertisement for Crestor (rosuvastatin) issued by AstraZeneca. Pfizer supplied Lipitor (atorvastatin).

The front cover of the leavepiece resembled a passport and bore a coat of arms which included the brand name Crestor. Pfizer considered that this, and not the Cresor logo on the inside page, was the most prominent display of the brand name and therefore the non- proprietary name should be immediately adjacent to it.

The Panel considered that the first mention of Crestor, on the front cover of the leavepiece, was the most prominent and therefore the non-proprietary name should have appeared immediately adjacent to this mention of the brand. A breach of the Code was ruled.

The journal advertisement showed a man jumping into a swimming pool alongside which was the claim '"Eureka" Discover a whole new level of cholesterol control'. The claim 'GET IT RIGHT FIRST TIME' appeared beneath the product logo in the bottom right hand corner.

Pfizer alleged that the claim 'Discover a whole new level of cholesterol control' could not be substantiated. The claim did not specify what was being compared eg 10mg of Crestor did not have superior cholesterol control to 80mg of atorvastatin. Even across the full dose range of Crestor there was no evidence of superiority to combination treatments such as simvastatin plus ezetimibe. Pfizer also alleged that the claim 'Get it right first time' was ambiguous and unqualified. Pfizer assumed that it referred to the use of 10mg of Crestor but at this dose Crestor did not have 'a whole new level' of control when compared to the dose ranges of other statins.

Pfizer alleged that 'cholesterol control' was ambiguous and unqualified, it did not know if it referred to total cholesterol, LDL, HDL or HDL/LDL ratio.

Prescribers would expect that 'whole new level' meant that the cholesterol control achieved with Crestor was associated with clinically significant improvements in cholesterol control. While AstraZeneca artificially selected a *mg for mg* comparison to demonstrate statistically significant differences in selected lipid parameters, there were no endpoint data to demonstrate that any differences were of clinical significance.

The Panel noted that Crestor was indicated *inter alia* for primary hypercholesterolaemia or mixed dyslipidaemia as an adjunct to diet when response to diet and other non-pharmacological treatments was inadequate.

With regard to Pfizer's allegation that the claim 'Discover a whole new level of cholesterol control' was misleading as it was not clear what was being compared, the Panel did not consider that readers would be confused or expect Crestor 10mg (the starting dose) to have superior cholesterol control to 80mg atorvastatin or that Crestor had superior cholesterol control to combination therapies. No other products were mentioned in the advertisement.

The Panel did not accept that the claim 'Get it right first time' was ambiguous and unqualified as alleged. The Panel noted AstraZeneca's submission with regard to the superiority of Crestor 10mg in reducing LDL over a range of start doses of other statins. The summary of product characteristics (SPC) stated that the majority of patients would be controlled at 10mg per day.

The Panel considered that although it might not be clear whether the claim 'Get it right first time' referred to the starting dose of Crestor, this was not necessarily a problem. AstraZeneca had data showing advantages for Crestor at 10mg and at 40mg. The achievement of targets at start dose was an advantage. In this regard the Panel noted that AstraZeneca had provided data with regard to the treatment of raised cholesterol and the under achievement of cholesterol targets with statins generally. AstraZeneca also had data showing advantages for 40mg Crestor compared to 80mg atorvastatin.

The Panel did not consider that the failure to define which type of cholesterol was meant in the term 'cholesterol control' was ambiguous and misleading as alleged. The term would be understood by the audience.

The Panel noted Crestor's licensed indication as stated above. The consequences of lowering cholesterol, ie endpoint data such as a reduction in coronary heart disease, were not licensed indications for Crestor. The Panel did not consider that the phrase 'whole new level' was a superlative nor would it be read in isolation as meaning that Crestor would be associated with clinically significant improvements in endpoint data as alleged. The difference would be the fact that more patients were treated to target with the starting dose than would be achieved by other statins.

The Panel did not accept that the claim 'Discover a whole new level of cholesterol control' was misleading, exaggerated or not capable of substantiation as alleged and thus ruled no breach of the Code.

Upon appeal by Pfizer, the Appeal Board noted AstraZeneca's submission that Crestor 10mg reduced LDL more than atorvastatin 10-20mg, simvastatin 20-40mg and pravastatin 10-40mg. Further that 82% of patients achieved a recognized European cholesterol target of <3mmol/L on Crestor 10mg compared with 51%, 48% and 16% of patients treated with atorvastatin 10mg, simvastatin 20mg and pravastatin 20mg respectively. The Crestor SPC stated that the majority of patients would be controlled at 10mg per day. The Lipitor SPC stated that 'The usual starting dose was 10mg. Doses should be individualised according to baseline LDL-C levels, the goal of therapy and patient response'.

In the Appeal Board's view 'cholesterol control' was a long-term outcome. Crestor received its UK

marketing authorization on 21 March 2003 and so long-term data on UK dosage patterns was not yet available. The Appeal Board noted AstraZeneca's submission at the appeal that it presently expected 80% of patients to achieve LDL control at 10mg daily. The Appeal Board noted that AstraZeneca had also cited three studies showing advantages for Crestor 40mg compared with atorvastatin 80mg; the results from two of these studies however were not available to AstraZeneca when the claim at issue was first used and the Appeal Board thus decided that neither would be taken into account during its consideration on this point. The Appeal Board considered that the achievement of LDL targets at start dose was an advantage: more patients were treated to target with the starting dose of Crestor than would be achieved by other statins. The Appeal Board noted, however, that the same magnitude of reduction in LDL observed with Crestor could be achieved with one or other of the other statins, albeit by upward titration from the starting dose if necessary.

The Appeal Board considered that the claim 'Discover a whole new level of cholesterol control' was a broad, unqualified claim. The lipid lowering ability of Crestor was not such as to constitute the significant improvement implied by the claim. The Appeal Board considered that the claim was misleading, exaggerated and not capable of substantiation as alleged and thus ruled breaches of the Code.

Pfizer considered that 'Eureka' implied a novelty for Crestor which could not be justified. Crestor's novelty with regard to efficacy and mode of action was one of potency alone; AstraZeneca had failed to demonstrate a clinical benefit of this claimed additional potency. Pfizer alleged that the use of Eureka could not be substantiated.

The Panel noted that the term 'Eureka' referred to a major discovery and meant 'I have found it'. The Panel did not consider that the discovery of Crestor would be seen as a major discovery similar to Archimedes' discovery of displacement. There was data showing advantages for Crestor over other statins but this was not of the degree of magnitude that would be implied by the use of the term 'Eureka'. The Panel considered that this aspect was misleading, incapable of substantiation and exaggerated as alleged. Breaches of the Code were ruled which were upheld on appeal by AstraZeneca.

Pfizer Limited complained about the promotion of Crestor (rosuvastatin) by AstraZeneca UK Limited. The items at issue were a passport style leavepiece (ref CRES020413576) and a journal advertisement (ref CRES120313340).

Pfizer supplied Lipitor (atorvastatin).

A Passport style leavepiece (ref CRES020413576)

The front cover of the leavepiece resembled a passport and bore a coat of arms which included the brand name Crestor. The ten page leavepiece, folded concertina style, was the same size as a passport.

COMPLAINT

Pfizer stated that the brand name Crestor appeared prominently as part of the crest on the front page. Pfizer disagreed with AstraZeneca's view that the Crestor logo on the inside page was the most prominent display of the brand name. Pfizer believed that the most prominent display of the brand name was on the front page and therefore that the non-proprietary name should be immediately adjacent to that. Pfizer alleged a breach of Clause 4.3 of the Code.

RESPONSE

AstraZeneca stated that as indicated by Pfizer, there had been inter-company discussions about the prominence of the brand name Crestor. AstraZeneca maintained that the first mention of the brand name was not necessarily the most prominent appearance of it and that clearly was the case with this leavepiece.

The passport carried an intricate crest with the name CRESTOR faded into the design. The most prominent features of the front cover were 'YOUR PASSPORT' and 'TO STATIN PRESCRIBING' which appeared above and below the crest. This encouraged the reader to open the item to reveal the inside spread.

Once inside the reader saw the familiar Crestor imagery and a highly prominent Crestor logo associated with the non-proprietary name and inverted black triangle which AstraZeneca believed to be the most prominent display of the brand name. There was no breach of Clause 4.3 of the Code.

This item had been superseded and was no longer in circulation.

PANEL RULING

The Panel noted that the first mention of the brand name was on the front cover of the leavepiece; it formed part of the coat of arms. When unfolding the piece the second mention appeared on page two and it also appeared in logo format on page three. The Panel accepted the principle that the first mention of a brand name was not necessarily the most prominent display of it. The format of the item was a relevant factor. In this instance the Panel considered that the first mention of the brand name was the most prominent and that the non-proprietary name should therefore have appeared immediately adjacent to this mention of the brand name on the front cover. The Panel thus ruled a breach of Clause 4.3 of the Code.

B Journal advertisement (ref CRES120313340)

The advertisement featured an illustration of a man jumping into a swimming pool alongside which appeared the claim '"Eureka" Discover a whole new level of cholesterol control'. The claim 'GET IT RIGHT FIRST TIME' appeared beneath the product logo in the bottom right hand corner of the advertisement.

1 Claims 'Discover a whole new level of cholesterol control' and 'Get it right first time'

COMPLAINT

Pfizer stated that it had serious concerns about the claim 'Discover a whole new level of cholesterol control'. Pfizer had tried to persuade AstraZeneca to modify or qualify this claim but without success. Pfizer disagreed with the arguments AstraZeneca had used to substantiate this claim which was widely used in promotional material for Crestor. Pfizer alleged that the claim was misleading.

The claim did not specify what was being compared. For example 10mg of Crestor did not have superior cholesterol control to 80mg of atorvastatin. Even across the full dose range of Crestor, there was no evidence of superiority to combination treatments such as simvastatin plus ezetimibe.

Pfizer alleged that the claim 'Get it right first time' was ambiguous and unqualified. Pfizer assumed, however, that it referred to the use of the 10mg dose of Crestor. At this dose Crestor did not have 'a whole new level' of control when compared to the dose ranges of other statins.

The term 'cholesterol control' was ambiguous and unqualified. Pfizer did not know if it referred to total LDL or HDL cholesterol or the HDL/LDL ratio.

Prescribers would expect with such a superlative as 'whole new level' that the cholesterol control achieved with Crestor would be associated with clinically significant improvements in cholesterol control. While AstraZeneca artificially selected a *mg for mg* comparison to demonstrate statistically significant differences in selected lipid parameters there were no endpoint data to demonstrate that any differences were of clinical significance.

The claim was not referenced to allow a prescriber to clarify the numerous ambiguities above.

Pfizer believed therefore that 'whole new level of cholesterol control' in association with Crestor could not be substantiated. Breaches of Clauses 7.2, 7.3, 7.4 and 7.10 of the Code were alleged.

RESPONSE

AstraZeneca stated that Pfizer's assumption that 'Get it right first time' referred to the 10mg dose was partly accurate as this was the licensed start dose for Crestor. However, it was also intended to indicate that Crestor should be the right choice of statin at initiation rather than using it in patients who had previously received an alternative statin. The advertisement did not contain any specific reference to the 10mg dose of Crestor.

As such, AstraZeneca did not accept that the claim implied that the advertisement related only to Crestor 10mg and therefore that AstraZeneca was creating the impression that Crestor 10mg was a new level of control over full dose ranges of statins.

AstraZeneca explained that there were two important elements to any comparison of cholesterol control. These were efficacy at initiation, and efficacy at maximal dose.

It was inappropriate to make the comparison suggested by Pfizer that the top dose of one statin should be compared to the start dose of another. It was also inappropriate to compare combinations of multiple treatment modalities to monotherapy.

However, AstraZeneca still proposed that the combination of Crestor with any other suitable treatment would still offer the potential for greater control.

AstraZeneca maintained that for either start dose or maximal dose comparisons Crestor offered significantly superior cholesterol lowering over other statins.

Efficacy at start dose was imperative when considering the requirements for effective cholesterol management. There were a number of studies that demonstrated this importance including the Euroaspire II and Performance for Life studies. These demonstrated the challenge facing the management of high-risk patients in need of effective cholesterol management. The Performance for Life study highlighted that up to December 2002 only approximately 50% of patients with established coronary heart disease (CHD), treated with initial doses of statins, achieved the National Service Framework (NSF) for CHD cholesterol target. Even with additional management there was still significant under achievement of targets. This demonstrated the need for a new level of cholesterol control.

Efficacy at start dose had considerable clinical relevance for patients and prescribers in the area of cholesterol management, which was dominated by evolving evidence-based guidelines and targets. Management of patients who did not achieve target was also highlighted by the Performance for Life study, which showed that 51% of patients did not receive therapy review with respect to the total cholesterol target of <5mmol/L and 66% did not receive review with respect to the need for a 25% reduction in total cholesterol. The importance for prescribers to effectively manage patients to these targets was further highlighted by the General Medical Services (GMS) contract, which rewarded practices for achieving specified cholesterol targets.

There was a wealth of data that demonstrated the statistically significant superiority in reducing LDL of Crestor 10mg over a range of start doses of other statins. The comparator doses included atorvastatin 10-20mg, simvastatin 20-40mg and pravastatin 10-40mg.

Therefore, the superiority of Crestor 10mg over traditional start doses of other statins offered the significant benefit of more patients achieving guideline targets in one visit. Clinical data demonstrated that 82% of patients achieved the European Atherosclerosis and other Societies (1998) LDL target of <3mmol/L on Crestor 10mg. This compared with 51%, 48% and 16% of patients treated with atorvastatin 10mg, simvastatin 20mg and pravastatin 20mg respectively.

AstraZeneca believed that such achievement of guideline targets provided the clinical relevance to support the claim and represented a meaningful new level of control, at start dose.

When considering the maximal doses of statins, Crestor offered a new level of cholesterol control.

Pfizer alleged that this was misleading because AstraZeneca was not specific with the term 'cholesterol control'. However, statins were generally considered as medicines to lower total and LDL cholesterol and Crestor 40mg demonstrated superiority over atorvastatin 80mg, the next most effective statin on these parameters.

This was demonstrated by a number of clinical trials. Data from trials CORALL and RADAR demonstrated that Crestor 40mg reduced LDL-C by 54% and 55% respectively compared to a reduction of 48% seen in both trials with atorvastatin 80mg.

AstraZeneca believed that this fulfilled a fundamental clinical need in delivering more high-risk patients to guideline targets than other statins.

Furthermore, neither of these comparisons were artificial mg for mg as they related to the important contrast of the lipid lowering effectiveness of appropriate comparative dosages.

PANEL RULING

The Panel noted that Crestor was indicated *inter alia* for primary hypercholesterolaemia or mixed dyslipidaemia as an adjunct to diet when response to diet and other non-pharmacological treatments was inadequate.

With regard to Pfizer's allegation that the claim 'Discover a whole new level of cholesterol control' was misleading as it was not clear what was being compared, the Panel did not consider that readers would be confused. It did not consider that readers would expect Crestor 10mg (the starting dose) to have superior cholesterol control to 80mg atorvastatin or that Crestor had superior cholesterol control to combination therapies. No other products were mentioned in the advertisement.

The Panel did not accept that the claim 'Get it right first time' was ambiguous and unqualified as alleged. The Panel noted AstraZeneca's submission with regard to the superiority of Crestor 10mg in reducing LDL over a range of start doses of other statins. The comparator doses included atorvastatin 10-20mg, simvastatin 20-40mg and pravastatin 10-40mg. Further that 82% of patients achieved the European Atherosclerosis and other Societies (1998) LDL target of <3mmol/L on Crestor 10mg. This compared with 51%, 48% and 16% of patients treated with atorvastatin 10mg, simvastatin 20mg and pravastatin 20mg respectively. The summary of product characteristics (SPC) stated that the majority of patients would be controlled at 10mg per day.

The Panel considered that although it might not be clear whether the claim 'Get it right first time' referred to the starting dose of Crestor, this was not necessarily a problem. AstraZeneca had data showing advantages for Crestor at 10mg and at 40mg. The achievement of targets at start dose was an advantage. In this regard the Panel noted that AstraZeneca had provided data with regard to the treatment of raised cholesterol and the under achievement of cholesterol targets with statins generally. AstraZeneca also had data showing advantages for 40mg Crestor compared to 80mg atorvastatin.

The Panel did not consider that the failure to define which type of cholesterol was meant in the term 'cholesterol control' was ambiguous and misleading as alleged. The term would be understood by the audience.

The Panel noted Crestor's licensed indication as stated above. The consequences of lowering cholesterol, ie endpoint data such as a reduction in coronary heart disease, were not licensed indications for Crestor. The Panel did not consider that the phrase 'whole new level' was a superlative nor would it be read in isolation as meaning that Crestor would be associated with clinically significant improvements in endpoint data as alleged. The difference would be the fact that more patients were treated to target with the starting dose than would be achieved by other statins.

The Panel did not accept that the claim 'Discover a whole new level of cholesterol control' was misleading, exaggerated or not capable of substantiation as alleged. The Panel thus ruled no breach of Clause 7.2, 7.4 and 7.10.

APPEAL BY PFIZER

Pfizer reiterated its original argument that the claim 'Discover a whole new world of cholesterol control' was ambiguous, misleading, incapable of substantiation and exaggerated and appealed the Panel's findings of no breach of Clauses 7.2, 7.4 and 7.10.

Pfizer noted that AstraZeneca had stated that the advertisement contained no specific reference to the 10mg start dose of Crestor. Pfizer alleged, therefore, that AstraZeneca was claiming that it was making this claim for Crestor at all doses. This was a wide claim and could not be justified at all doses.

Pfizer noted that at a start dose of 10mg only, as AstraZeneca conceded, better control could be achieved with 40mg of atorvastatin. At 20mg of Crestor, there was no advantage over 80mg of atorvastatin. Pfizer stated that since it had submitted its complaint, the 40mg dose of Crestor had become unavailable in primary care for initiation without specialist supervision and referred to recent letters sent by AstraZeneca to health professionals at the behest of the Medicines and Healthcare products Regulatory Agency and Committee on Safety of Medicines. Even in those situations where 40mg was used, there was no evidence to suggest that the cholesterol lowering effects of Crestor were in anyway superior to a combination of a statin and ezetimibe. AstraZeneca's assertion that it was inappropriate to compare combinations of multiple treatment modalities to monotherapy required justification. Pfizer alleged that if AstraZeneca was stating that comparisons between monotherapy statins only were justifiable, then its advertisement must be qualified accordingly.

Pfizer stated that the Panel did not appear to have noted that the start dose of atorvastatin was not limited to 10mg and 20mg and therefore appeared to accept that Crestor offered specific advantages at its starting dose. The mg for mg comparison with regard

to percentage of patients achieving European Atherosclerosis and other Societies (1998) LDL target was therefore invalid. Further, the Panel had juxtaposed the two sentences 'AstraZeneca had data showing advantages for Crestor at 10mg and 40mg' and 'The achievement of targets at start dose was an advantage' which suggested that there might be some misunderstanding about the start dose of Crestor, which was 10mg (as above). The efficacy of the 40mg dose of Crestor was irrelevant in this context.

Pfizer stated that the Performance for Life study was used to demonstrate the apparent failure of statins to treat patients to target. The ability of Crestor to change this was speculative. It was more a reflection of clinicians' unwillingness to use appropriate start doses of statins and to titrate dosage on the basis of subsequent cholesterol measurement. It possibly also reflected the inability of experts and of pharmaceutical manufacturers to convince prescribers of the need to treat to target. This latter concept was relatively new in the primary care management of hyperlipidaemia.

COMMENTS FROM ASTRAZENECA

AstraZeneca submitted that Pfizer's appeal indicated that it did not accept the Panel's opinion that health professionals would intuitively understand the advertisement and make the appropriate comparisons. AstraZeneca submitted that with this in mind it struggled to understand which comparisons Pfizer believed were ambiguous, misleading, incapable of substantiation or exaggerated. This seemed to be based on a counter-intuitive premise that it was appropriate to compare the start dose of one medicine with various doses of another or with multiple medicines used in combination.

AstraZeneca maintained its previous position that there were only two important elements to any comparison of cholesterol control ie efficacy at initiation (being the licensed usual start dose) and efficacy at maximal dose.

AstraZeneca submitted that efficacy in combination was an additional element to cholesterol control and it referred to the example of ezetimibe suggested by Pfizer. According to the licence for ezetimibe it should be used in patients who were not appropriately controlled with a statin alone or who failed to tolerate statin therapy.

However AstraZeneca submitted that if it was considering statin usage in combination therapy, it would still propose that the combination of Crestor with any other suitable treatment would still offer the potential for greater control.

AstraZeneca noted that Pfizer had questioned the relevance of data from studies such as Performance for Life that demonstrated the challenge facing physicians managing patients at high risk of cardiovascular disease. Pfizer had claimed that the under treatment demonstrated in this study was due to physicians not choosing to use appropriate start doses and titrate. AstraZeneca submitted that it had reflected the accepted view that it was entirely appropriate for physicians to initiate the licensed usual start doses of statins and up-titrate, instead of second-guessing the dose that was required. AstraZeneca submitted that it therefore endorsed the Panel's opinion that a comparison to doses higher than 10mg and certainly 20mg of atorvastatin should not be the focus of Pfizer's counter argument. The effort involved in patient review and up titration was more likely to be the reason behind the relative under achievement of targets.

AstraZeneca submitted that there was a wealth of data that demonstrated the superiority of Crestor 10mg in reducing LDL compared with usual start doses of other statins. These doses included atorvastatin 10-20mg and simvastatin 20-40mg. Fundamentally Crestor 10mg resulted in more patients achieving guideline targets in one visit than other statins as generally used and such achievement was highly relevant in a therapy area dominated by targets.

AstraZeneca submitted that when considering the maximal doses of statins it considered that the patient group needed to be considered carefully. Both the Crestor and Lipitor SPCs suggested that these were likely to be patients with severe hypercholesterolaemia at high cardiovascular risk. It was therefore appropriate for these doses to be used in conjunction with a specialist in order for patients to be optimally managed. Pfizer's statement that Crestor 40mg had become 'unavailable' in primary care without such supervision raised additional concerns on how it would choose to brief its salesforce.

AstraZeneca submitted that for this important but relatively small group of patients Crestor did offer a new level of cholesterol control and the possibility for some of them to achieve target without combination therapy. This was demonstrated by a number of clinical trials including patients with heterozygous familial hypercholesterolaemia and diabetes.

AstraZeneca considered that this had fulfilled the fundamental clinical need of delivering more high-risk patients to guideline targets than other statins and justified the claim 'Discover a whole new level of cholesterol control'.

FURTHER COMMENTS FROM PFIZER

Pfizer alleged that the claim 'Discover a whole new level of cholesterol control' was a broad claim and could not be used in an unqualified manner. In its original response, AstraZeneca had separated the issues of cholesterol control into efficacy at initiation and efficacy at maximal dosage. No such distinction was made in the advertisement. Thus the claim must be taken across the board, and Pfizer alleged that it did not stand up to scrutiny in either situation.

Pfizer stated that it was surprised by AstraZeneca's statement that there were only two important elements to any comparison of cholesterol control ie efficacy at initiation and efficacy at maximal dose. This was simplistic and failed to take account of safety, tolerability, concordance and the benefit:risk ratio.

Pfizer stated that at initiation, atorvastatin could be used at higher doses and, across its starting dose

range, offered better 'cholesterol control' than the starting dose of any other statin. Moreover, thereafter it offered better cholesterol control across the dose range useable in primary care.

Pfizer stated that it had found a lack of compatibility in AstraZeneca's argument that most patients were to be started on 10mg of Crestor and then the GP, by implication, did not need to review them, safe in the knowledge that they would have their cholesterol under control and those patients with high cholesterol should, in any case, be under the care of a specialist.

Pfizer noted that the GMS contract and the monitoring of achievement of targets in general demanded measurement of cholesterol, which must be performed and reviewed under the auspices of the prescribing physician. To recommend such a 'treat and hope' philosophy was unacceptable.

Pfizer stated that the Panel had failed to acknowledge that alternative start dosing with atorvastatin offered superior cholesterol control to Crestor 10mg. AstraZeneca had compounded this by introducing, in its appeal, the word 'usual', to qualify this claim, into its discussions of start dose. AstraZeneca's did not refer to the 'usual' start dose in its response. Pfizer alleged that in any case, the 'usual' start dose was irrelevant in this context. Even if it were considered relevant, the claim would have to be modified accordingly. Pfizer did not however, consider that the licensed start dose was the point at issue.

Pfizer alleged that AstraZeneca's statement that more patients achieved guideline targets after one visit with Crestor 10mg than with other statins as generally used was hypothetical, apparently based on the comparison of separate data sets: the Performance for Life study and data derived from randomised controlled trials (RCTs) of Crestor. Cholesterol lowering in RCTs could not be assumed in such an unqualified way to translate into the attainment of treatment targets in real life, or indeed in an improvement in clinical outcomes, an area in which AstraZeneca could present no useful data.

Pfizer did not understand AstraZeneca's penultimate paragraph which appeared to attribute a special quality to Crestor in the treatment of high risk patients; to Pfizer's knowledge no such claim for superior outcome could be made for Crestor with this group of patients.

Pfizer stated that the method by which it briefed its sales force was not at issue.

APPEAL BOARD RULING

In relation to the claim 'Discover a whole new level of cholesterol control' the Appeal Board noted AstraZeneca's submission that Crestor 10mg reduced LDL more than atorvastatin 10-20mg, simvastatin 20-40mg and pravastatin 10-40mg. Further that 82% of patients achieved the European Atherosclerosis and other Societies (1998) LDL cholesterol target of <3.0mmol/L on Crestor 10mg compared with 51%, 48% and 16% of patients treated with atorvastatin 10mg, simvastatin 20mg and pravastatin 20mg respectively. The Crestor SPC stated that the majority of patients would be controlled at 10mg per day. The Lipitor SPC stated that 'The usual starting dose was 10mg. Doses should be individualised according to baseline LDL-C levels, the goal of therapy and patient response'.

In the Appeal Board's view 'cholesterol control' was a long-term outcome. Crestor received its UK marketing authorization on 21 March 2003 and so long-term data on UK dosage patterns was not yet available. The Appeal Board noted AstraZeneca's submission at the appeal that it presently expected 80% of patients to achieve LDL control at 10mg daily. The Appeal Board noted that AstraZeneca also had data showing advantages for Crestor 40mg compared with atorvastatin 80mg; Jones *et al*, the CORALL study (Franken *et al*, 2004) and the RADAR study (Jukema *et al*, 2004). Neither the CORALL study nor the RADAR study were available to AstraZeneca when the claim at issue was first used and the Appeal Board thus decided that neither would be taken into account during its consideration on this point. The Appeal Board considered that the achievement of LDL cholesterol targets at start dose was an advantage: more patients were treated to target with the starting dose of Crestor than would be achieved by other statins. The Appeal Board noted, however, that the same magnitude of reduction in LDL observed with Crestor could be achieved with one or other of the other statins, albeit by upward titration from the starting dose if necessary.

The Appeal Board considered that the claim 'Discover a whole new level of cholesterol control' was a broad, unqualified claim. The lipid lowering ability of Crestor was not such as to constitute the significant improvement implied by the claim. The Appeal Board considered that the claim was misleading, exaggerated and not capable of substantiation as alleged. The Appeal Board thus ruled breaches of Clauses 7.2, 7.4 and 7.10. The appeal on this point was successful.

2 Claim 'Eureka'

COMPLAINT

Pfizer alleged that the use of the term 'Eureka', an attributed quote from Archimedes in ancient Greek, referring to a major discovery (of displacement), implied a novelty for Crestor, which could not be justified. Crestor's novelty with regard to efficacy and its mode of action was one of potency alone. As Pfizer had stated in point B1 above, AstraZeneca had failed to demonstrate a clinical benefit of this claimed additional potency.

Pfizer believed that the term 'Eureka' could not be substantiated. Breaches of Clauses 7.2, 7.3, 7.4 and 7.10 were alleged.

RESPONSE

AstraZeneca noted that Pfizer had alleged that the novelty of Crestor was one of mg for mg potency alone and that no clinical benefit for this had been shown. AstraZeneca submitted that it highlighted above the clinical relevance for the superior efficacy at start dose.

Patients achieved lower cholesterol levels and more patients achieved recommended cholesterol targets in one visit than with the recommended start doses or even the usual doses of other statins. Current practice still reflected a prescriber's preference to start at low dose and titrate upwards rather than to initiate at higher doses.

Furthermore, even with initiation at higher doses of other statins, Crestor 10mg continued to offer superior LDL lowering than atorvastatin 20mg, pravastatin 40mg and simvastatin 40mg. Data from the STELLAR study demonstrated that Crestor 10mg reduced LDL by 46%, which was significantly superior to the reductions of 37%, 39% and 30% seen with atorvastatin 10mg, simvastatin 40mg and pravastatin 40mg respectively. Data from the CORALL and RADAR studies demonstrated LDL reductions of 46% and 44% respectively for Crestor 10mg compared to 41% and 38% respectively for atorvastatin 20mg.

Additional practical advantage was granted by the fact that this superior LDL lowering was achieved at a cost reduction of £11.66 against atorvastatin 20mg and pravastatin 40mg, and £2.97 against the generic Drug Tariff price of simvastatin 40mg, based on treatment for 28 days.

In summary, AstraZeneca believed that the: additional LDL lowering efficacy at start dose; enhanced achievement of National and International Guideline targets; reduced prescriber burden in terms of the need for patient review and up-titration and; favourable cost-effectiveness comparison all underpinned the sense of discovery a prescriber might feel when prescribing Crestor. AstraZeneca's use of the word 'Eureka' was designed to highlight this.

As such AstraZeneca did not believe the use of the term 'Eureka' was misleading, exaggerated or unsubstantiated.

PANEL RULING

The Panel noted that the term 'Eureka' referred to a major discovery and meant 'I have found it'. The Panel did not consider that the discovery of Crestor would be seen as a major discovery similar to Archimedes' discovery of displacement. There was data showing advantages for Crestor over other statins but this was not of the degree of magnitude that would be implied by the use of the term 'Eureka'. The Panel considered that this aspect was misleading, incapable of substantiation and exaggerated as alleged. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled. This ruling was appealed by AstraZeneca.

APPEAL BY ASTRAZENECA

AstraZeneca noted the Panel's comment that the exclamation was attributed to Archimedes and related to his discovery of displacement and should only be used in conjunction with such a major discovery.

AstraZeneca submitted that Eureka literally meant 'I have found it', derived from the greek verb, heurisk_, which meant to find. There had been many uses of the term since its use by Archimedes and 'Eureka' was now part of modern language and as such, the origin of the word was of interest but not relevant. The word did not have to relate to a major discovery and indeed Archimedes himself did not believe that his discovery of the principle of displacement was his greatest discovery.

AstraZeneca submitted that the modern usage was exemplified by dictionary definitions such as 'a cry of joy or satisfaction when one finds or discovers something' (Oxford) or 'an exclamation of triumph on discovering or solving something' (Collins).

AstraZeneca submitted that this was further supported by the widespread use of Eureka in the promotion of goods. An Internet search identified 1,750,000 examples of the term being used commercially. These varied from a children's interactive museum, housing and real estate, discount shopping and a tent company through to a range of vacuum cleaners.

AstraZeneca noted that the Panel had accepted that there was sufficient evidence to support the claim 'Discover a whole new level of cholesterol control' and there remained a significant need for this new level of control. Studies had highlighted that before Crestor only approximately half of patients treated with statins achieved recommended healthy cholesterol levels. As guidelines continued to drive the recommended healthy levels to lower targets prescribers would increasingly need to discover new levels of control.

AstraZeneca submitted that supporting this there was a wealth of data that demonstrated the statistically significant superiority in reducing LDL and delivering patients to healthy cholesterol levels of Crestor 10mg compared to a range of start doses of other statins. The comparator doses included atorvastatin 10-20mg, simvastatin 20-40mg and pravastatin 10-40mg. Crestor offered at least a one dose titration advantage over all statins with a 2 or 3 dose titration advantage over simvastatin or pravastatin.

AstraZeneca submitted, based on the modern use of Eureka, the above definitions and the clinical evidence, that Eureka was a wholly appropriate way to describe the feeling a prescriber or patient might experience on discovering the effectiveness of Crestor. As such the use of this expression was not misleading, exaggerated and unsubstantiated.

COMMENTS FROM PFIZER

Pfizer maintained that 'Eureka' implied a discovery worthy of note and therefore attempted to differentiate Crestor from other statins. Pfizer did not consider that the commercial use of Eureka in any way reduced the power of its meaning – that was a real 'discovery' of something novel and different. Pfizer alleged that the use of the expression was factually incorrect for the reasons outlined below.

Pfizer alleged that the claim that only approximately half of patients reached target levels of cholesterol on existing statins was misleading and it could provide evidence to show that 96% of patients treated with atorvastatin achieved the Joint British Recommendations and General Medical Service's

Contract total cholesterol target of 5mmol/L or less (Athyros *et al* 2002). In addition, there was data demonstrating that between 87-95% of patients treated with atorvastatin in clinical trials reached the National Cholesterol Education Program Adult Treatment Panel's (NCEP ATPIII) LDL cholesterol target of <2.6mmol/L (McKenney *et al* 2004, Jones *et al* 2003), levels that were currently lower than those required by the GMS contract.

Pfizer noted that AstraZeneca had implied that as targets were lowered physicians would find the efficacy of established statins increasingly inadequate and therefore need to discover new levels of control. In support of this argument AstraZeneca had claimed that there was a wealth of data demonstrating the clinical superiority of Crestor 10mg in reducing LDL. Pfizer alleged that this was misleading in that the comparison was not made to the possible range of doses of established statins that could be initiated, dependent on the initial cholesterol levels and the reduction that was required. Pfizer stated that there was no significant superiority of Crestor 10mg over atorvastatin 20 to 40mg (Law *et al* 2003, Bays *et al* 2004).

Pfizer alleged that furthermore there was no clear indication on the advertisement as to whether this claim was in reference to statins used as monotherapy or whether this remained true for statins used in combination. Pfizer stated that statins used in combination with other compounds such as ezetimibe provided cholesterol control surpassing that of Crestor 10mg (Ballantyne *et al* 2004, Guadiani *et al* 2004, AstraZeneca 'Dear Healthcare Professional' letter, 2004). Should AstraZeneca defend this point by stating that any comparison should be made with statins as a monotherapy only, its claim should then be so qualified in the advertisement.

Pfizer stated that the claim of the dose titration advantage of Crestor assumed a milligram for milligram comparison, rather than using doses of equivalent efficacy and did not reflect clinical practice; if appropriate doses were used, Crestor did not offer a superior level of control to other established statins (Law *et al*, Bays *et al*, Ballantyne *et al*).

Pfizer noted that AstraZeneca had not referred to recent changes in its SPC that outlined significant restrictions on the use of Crestor. These restrictions included a re-emphasis of the approved start dose of 10mg and also described patient populations in whom the use of Crestor was specifically contraindicated. The prevention of the use of the 40mg dose of Crestor in primary care and its restriction to use within secondary care only further undermined AstraZeneca's right to claim a significant discovery by the use of 'Eureka'. In the light of the recent letters sent to all health professionals and pharmacists in the UK as well as in other countries advising them of these limitations, Pfizer considered that the statement 'Eureka' was not representative of the clinical limitations placed upon the use of Crestor, especially in primary care.

In summary, Pfizer restated that the use of 'Eureka' in proclaiming the discovery of Crestor could not be justified and that the Panel was correct in its finding of breaches of Clauses 7.2, 7.4 and 7.10.

APPEAL BOARD RULING

In the Appeal Board's view 'Eureka' referred to a major discovery. This was reinforced by the illustration of the man jumping for joy into a swimming pool. The Appeal Board did not consider that the discovery of Crestor would be seen as a major discovery; whilst there was data showing advantages for Crestor over other statins this was not of the degree of magnitude that would be implied by 'Eureka'. The Appeal Board considered that the use of 'Eureka' was misleading, incapable of substantiation and exaggerated as alleged and so it upheld the Panel's ruling of breaches of Clauses 7.2, 7.4 and 7.10. The appeal on this point was unsuccessful.

Complaint received **6 April 2004**

Case completed **3 August 2004**

CASE AUTH/1579/4/04

GLAXOSMITHKLINE v ASTRAZENECA

Symbicort leavepiece

GlaxoSmithKline complained that claims for Symbicort (formoterol/budesonide) were not substantiated by the cited reference, the SUND (Symbicort Up aNd Down) study. The item at issue was a four page leavepiece issued by AstraZeneca which had been sent as a mailing to health professionals. GlaxoSmithKline supplied Seretide salmeterol/fluticasone).

GlaxoSmithKline noted that in its previous complaint about promotional activity in relation to the SUND study, Case AUTH/1527/10/03, the study was not specifically reviewed, and the Panel had noted that AstraZeneca had not defended it. AstraZeneca had continued to make superiority claims for Symbicort adjustable dosing over Seretide fixed dosing, based upon its analysis of the SUND study. GlaxoSmithKline alleged that these claims were not substantiable based upon the design of the study and the fact that the primary endpoint (well controlled asthma weeks) showed no difference between the study arms.

The claims of specific concern, which appeared in the leavepiece at issue, were (1) Adjustable Symbicort ahead by 40% in severe exacerbation control: study confirms adjustable dosing is better than Seretide fixed dosing, (2) Symbicort superior to Seretide in severe exacerbation control: patients shown to be better controlled on adjustable dosing and (3) Patients on adjustable Symbicort benefited from 40% fewer severe exacerbations (p=0.018) compared with fixed-dose Seretide according to a recent study. GlaxoSmithKline noted that the fixed dose treatment arms in the SUND study lasted 7 months; the 7 month Symbicort adjustable dose arm however included 1 month of fixed dosing and 6 months of adjustable dosing.

GlaxoSmithKline noted that AstraZeneca had claimed a 40% reduction in severe exacerbations for Symbicort adjustable dosing compared with Seretide fixed dosing, by calculating the number of exacerbations in each arm over the total study period. In this period however, a combination of both fixed and flexible dosing was used in the Symbicort adjustable dosing arm. To describe 1 month of fixed dosing plus 6 months of adjustable dosing as 'the adjustable dosing arm' was misleading. GlaxoSmithKline alleged that the claim of a 40% reduction in severe exacerbations for adjustable dosing was thus inaccurate, unbalanced and not capable of substantiation.

GlaxoSmithKline noted that the primary endpoint of the SUND study was defined as the odds of achieving a well-controlled asthma week. This was a composite measure of asthma control, which included asthma exacerbations. The study showed that there was no statistical significance in the primary endpoint between any of the arms of the study, yet superiority had been claimed for the primary endpoint of control ('patients shown to be better controlled on adjustable dosing') in the second half of claim 2 above. This did not reflect the primary outcome of the study. Additionally, the data on exacerbations was one of many secondary measures that the study was not appropriately powered to examine and was at risk from statistical multiplicity. Thus the 40% claim was not capable of substantiation and did not reflect the available evidence.

GlaxoSmithKline noted that exacerbations were defined as the use of oral steroids, visits to emergency room or hospitalisations. When their asthma worsened patients in the flexible dosing arm could increase their study medication. This, however, was not an option available to those in the fixed dose arm, who were required to take oral steroids. The study was thus inherently biased and this would have resulted in an over-reporting of exacerbations in the fixed dose group as compared to the adjustable dosing group.

In summary, GlaxoSmithKline alleged that the claims were misleading because the fundamental study design was not robust and suffered from inherent bias; the primary endpoint failed to meet statistical significance.

The Panel noted that two of the three claims at issue had been incorrectly cited by GlaxoSmithKline. The first headline claim read 'Symbicort ahead by 40% in severe exacerbation control:' followed immediately in smaller print by 'study confirms adjustable dosing is better than Seretide fixed dosing'. GlaxoSmithKline had incorrectly inserted 'Adjustable' at the beginning of the claim. The second claim read 'Symbicort superior to Seretide in severe exacerbation control: patients shown to be better controlled on adjustable Symbicort'. GlaxoSmithKline had incorrectly replaced the final 'Symbicort' with 'dosing'. The final claim, 'Patients on adjustable Symbicort benefited from 40% fewer severe exacerbations (p=0.018) compared with fixed dose Seretide according to a recent study' had been correctly cited.

The Panel noted that the SUND study was designed to determine whether adjustable dosing with Symbicort had greater efficacy compared to fixed dose regimens with Seretide or Symbicort. There were three treatment periods: run-in, double blind and a six month open extension during which patients received Seretide (one inhalation bid) or a fixed dose of Symbicort (two inhalations) or an adjustable dose of Symbicort (one or two inhalations bid, depending on the level of asthma control). The primary endpoint was the odds of having a well controlled asthma week during the post-randomisation period; a well controlled asthma week was defined as a week with no night-time awakenings due to asthma, no exacerbations and no change in asthma treatment due to adverse events plus at least two of the following: asthma symptom score of >1 on ≤ 2 days; ≤ 2 days of reliever medication use; morning PEF ≥ 80% of the predicted normal value every day. Exacerbations were defined as oral steroid treatment for ≥ 3 days, emergency room visits and/or hospitalisation.

The study showed that the odds of achieving a well controlled asthma week over the whole treatment

period were similar for fixed dose Seretide and adjustable dosed Symbicort. One fifth across all groups failed to achieve a well controlled asthma week throughout the study period. There were no treatment differences observed for total asthma control weeks.

Patients receiving adjustable dose Symbicort had 40% fewer exacerbations than those receiving fixed dose Seretide (35 vs 59, p=0.018). The authors stated that this treatment difference related to a reduction of 20 severe exacerbations per 100 patients/year (numbers needed to treat – 4.9). The total rate of exacerbations over 7 months for Symbicort and Seretide was 0.024/month and 0.41/month respectively, ie a rate reduction of 39.7% (p=0.018) in favour of adjustable dose Symbicort. The results also showed that 57% of those taking adjustable dose Symbicort required no step-ups in treatment. Most patients who needed a temporary step-up regained control of their asthma in 7 days (67% of the step-up periods).

The study authors noted that with increasing study duration Symbicort appeared to provide better asthma control: the favourable difference in exacerbation rates became more marked over time. However the use of well controlled asthma weeks alone only presented half the picture of a successful treatment outcome. The results highlighted the need for studying multiple measures of asthma control before drawing conclusions on the effectiveness of different regimens. Promptly increasing the dose of inhaled corticosteroid and long acting B2 agonists at the first sign of asthma worsening provided an early intervention strategy for the reduction of exacerbations.

The design of the SUND study allowed Symbicort patients to increase their dose of steroid by using more of the same inhaler. Adjustable dosing with Seretide was only possible by using an additional inhaler to increase the dose of inhaled corticosteroid because the salmeterol dose response curve was limited. The Panel noted that AstraZeneca had submitted a report which addressed the allegation that the study design was biased as fixed dose arms only had the option to use oral steroids if their asthma worsened. The report explained that this was not the case; oral steroids were not used for self management but were only given by clinicians as a rescue medication if patients needed to consult them because of severe asthma attack. Symbicort patients, who increased their maintenance treatment in response to an increased need for relief medication had less unscheduled clinic visits because of exacerbations that then resulted in less oral steroid use and emergency treatment.

The Panel noted that the leavepiece concentrated wholly on the severe exacerbation data from the SUND study. This was only one aspect of asthma control. The only reference in the leavepiece to the primary endpoint of the study was a statement at the bottom of a bar chart, which took up the whole of page 3, that 'The primary endpoint (odds of a well-controlled asthma week) showed no significant difference between the treatment arms'. The Panel considered that by focussing solely on exacerbation data the leavepiece did not give a balanced and fair overview of the comparison of adjustable dose Symbicort and fixed dose Seretide. In the Panel's view some readers might be misled and assume that in all aspects of asthma control Symbicort was better than Seretide which was not the case. This impression was compounded by a caption to a photograph on the back page which stated 'She missed the sales last year – now, after gaining control with adjustable Symbicort, she can enjoy shopping without symptoms'. The Panel thus concluded that given the context in which they appeared the claims 'Symbicort ahead by 40% in severe exacerbation control: study confirms adjustable dosing is better than Seretide fixed dosing', 'Symbicort superior to Seretide in severe exacerbation control: patients shown to be better controlled on adjustable Symbicort' and 'Patients on adjustable Symbicort benefited from 40% fewer severe exacerbations (p=0.018) compared with fixed dose Seretide according to a recent study' were not a fair reflection of the outcome of the SUND study. The claims were misleading in this regard and thus could not be substantiated. Breaches of the Code were ruled.

GlaxoSmithKline UK Ltd complained about the promotion of Symbicort (formoterol/budesonide) by AstraZeneca UK Limited. It was concerned that certain claims were not substantiated by the cited reference, the SUND (Symbicort Up aNd Down) study. The item at issue was a four page leavepiece (ref SYMB 03 13214B) which had been sent as a mailing to health professionals in February 2004. GlaxoSmithKline supplied Seretide (salmeterol/fluticasone). Dialogue between the companies had failed to resolve the issues.

COMPLAINT

GlaxoSmithKline noted that it had previously complained about promotional activity in relation to the SUND study, Case AUTH/1527/10/03, wherein the study was not specifically reviewed, and the Panel had noted that AstraZeneca had not defended it. Since Case AUTH/1527/10/03 AstraZeneca had continued to make superiority claims for Symbicort adjustable dosing over Seretide fixing dosing, based upon its analysis of the SUND study. GlaxoSmithKline alleged that these claims were not substantiable based upon the design of the study and the fact that the primary outcome parameter (well controlled asthma weeks) showed no difference between the study arms. In order to address these superiority claims it was necessary to critically review the design and analysis of the SUND study. GlaxoSmithKline provided a copy of a report from an independent asthma expert who had critically reviewed the SUND study.

The claims of specific concern, which appeared in the leavepiece at issue, were:

1 'Adjustable Symbicort ahead by 40% in severe exacerbation control: study confirms adjustable dosing is better than Seretide fixed dosing.'

2 'Symbicort superior to Seretide in severe exacerbation control: patients shown to be better controlled on adjustable dosing.'

3 'Patients on adjustable Symbicort benefited from 40% fewer severe exacerbations (p=0.018) compared with fixed-dose Seretide according to a recent study.'

In relation to claims 1 and 3 GlaxoSmithKline had asked AstraZeneca to clarify the time periods over which exacerbation numbers were measured for adjustable dosing with Symbicort and fixed dosing with Seretide. AstraZeneca had explained that all treatment arms in the SUND study lasted 7 months; the 7 month Symbicort adjustable dose arm included 1 month of fixed dosing and 6 months of adjustable dosing. The other two treatment arms were fixed dose for all 7 months.

GlaxoSmithKline noted that AstraZeneca had claimed a 40% reduction in severe exacerbations for Symbicort adjustable dosing compared with Seretide fixed dosing, by calculating the number of exacerbations in each arm over the total study period. In this period however, a combination of both fixed and flexible dosing was used in the Symbicort adjustable dosing arm. Thus, describing 1 month of fixed dosing together with 6 months of adjustable dosing as 'the adjustable dosing arm' was misleading. GlaxoSmithKline alleged that the claim of a 40% reduction in severe exacerbations for adjustable dosing was thus inaccurate, unbalanced and not capable of substantiation.

In relation to all three claims GlaxoSmithKline was concerned about flawed statistical analysis and interpretation of the SUND study.

GlaxoSmithKline noted that the primary endpoint of the SUND study was defined as the odds of achieving a well-controlled asthma week. This was a composite measure of asthma control, which included asthma exacerbations. The study showed that there was no statistical significance in the primary endpoint between any of the arms of the study. Despite this lack of significance, superiority had been claimed for the primary endpoint of control ('patients shown to be better controlled on adjustable dosing') in the second half of claim 2 above. This was not reflective of the primary outcome of the study. Additionally, the data on exacerbations was one of many secondary measures that the study was not appropriately powered to examine and was at risk from statistical multiplicity. Thus the 40% claim was not capable of substantiation or reflective of the available evidence.

GlaxoSmithKline also alleged that the study design was biased towards favouring adjustable dosing when measuring exacerbations. Exacerbations were defined as the use of oral steroids, visits to emergency room or hospitalisations. When their asthma worsened patients in the flexible dosing arm could increase their study medication. This, however, was not an option available to those in the fixed dose arm, and as such they were required to take oral steroids. The study was thus inherently biased against fixed dosing in the evaluation of this parameter. This would have resulted in an over-reporting of exacerbations in the fixed dose group as compared to the adjustable dosing group.

GlaxoSmithKline considered that, in reviewing the points above, the SUND study design was not robust, with inherent bias, and prevented superiority claims being made for Symbicort adjustable dosing over Seretide fixed dosing. It was an open label study, which compared two treatment regimens ie fixed and adjustable dosing and not two medicines directly. Despite these flaws, superiority claims had been made. This was seen both in claims of being 'better controlled', and on 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. GlaxoSmithKline noted that no statistical analysis had been provided for this claim.

In summary, GlaxoSmithKline alleged that the claims were misleading in breach of Clauses 7.2, 7.3 and 7.4 of the Code because the fundamental study design was not robust and suffered from inherent bias and the primary endpoint failed to meet statistical significance.

RESPONSE

AstraZeneca stated that the SUND study was an important study in the context of current UK clinical practice. The use of combination inhalers in the UK was increasing and represented 25% of total asthma prescribing. Doctors needed to be able to make a choice on which combination to prescribe. The British Thoracic Society guidelines recommended the use of inhaled steroids and long-acting beta agonists (LABA) at step 3 of asthma management. Combination inhalers allowed both these agents to be given in a single inhaler and might assist in patient compliance. In the last few years there had been an increase in prescriptions in the UK for these products. There were currently only two combination inhalers available in the UK, Symbicort and Seretide.

AstraZeneca submitted that there were clear differences in the pharmacology of the components of Symbicort and Seretide (Palmqvist *et al* 1999 and Palmqvist *et al* 1997). Symbicort Turbohaler was licensed in adults to be given between the dose ranges of one inhalation daily to four inhalations twice daily. This range of adjustability within a single inhaler was due to the unique properties of the LABA within Symbicort, formoterol. Formoterol had a greater range of dose responsiveness than the LABA constituent (salmeterol) in Seretide (Palmqvist *et al* 1999). This range of dose-responsiveness meant a higher dose of formoterol would produce a higher clinical response. For the patient this meant that if they increased their dose they would receive an increased effect. Increasing doses of salmeterol did not produce this same increase in clinical response. The other difference between formoterol and salmeterol was their onset of action. Formoterol had an onset of action as fast as salbutamol (within 3 minutes), the most widely used reliever medication, while maintaining effect for 12 hours; salmeterol's onset of action was within 15 minutes (again being maintained for 12 hours)(Palmqvist *et al* 1997). These properties allowed adjustability of the dose within a single inhaler of Symbicort, compared with Seretide where a new or additional inhaler was required to make a dosage alteration during worsening of asthma.

AstraZeneca noted that previous studies comparing adjustable Symbicort with fixed dose Symbicort had shown that allowing patients to increase their dose of inhaled steroid and long-acting beta agonists via a combination inhaler when symptoms increased (as part of an asthma action plan) led to fewer asthma exacerbations (FitzGerald *et al* 2003 and Ställberg *et al* 2003). The next important clinical question was to compare Seretide with the adjustable dosing regimen of Symbicort.

AstraZeneca submitted that for these reasons, SUND was an important study that helped doctors to make a decision on which combination inhaler to prescribe. The study was clinically relevant; in terms of its design and results it reflected real-life clinical practice.

In clinical practice, patients on Seretide had three options when their asthma symptoms increased. They could increase the intake of reliever medication and progress on to oral steroids if an exacerbation developed; switch to an increased strength Seretide inhaler; take an additional Flixotide inhaler along with the Seretide dose. The basis of these options was to increase the dose of inhaled steroid because, as discussed above, there was no clinical benefit to increasing the salmeterol component. AstraZeneca noted that adjustable dosing with Seretide within a single inhaler was outside the product licence.

AstraZeneca submitted that prescribing data from Mediplus suggested that the first option was what happened in clinical practice; from March 2003 to March 2004 only 4.3% and 9.4% of patients on Seretide Accuhalers and Evohalers respectively received a prescription for more than one strength of inhaler. During this same time period only 12.8% of patients received prescriptions for both Seretide and Flixotide. The data did not indicate how many of these were concurrent prescriptions. Mediplus was used industry wide and was accepted as the most reliable source of UK prescribing data. It was a database of 3.5 million patient records taken form the electronic records of 800 GPs and reported longitudinal treatment decisions for patients. AstraZeneca submitted that this information was backed up by anecdotal evidence from practising doctors in the UK.

AstraZeneca noted that for these reasons the first option was the one that was available to patients in the Seretide arm in the SUND study as it was designed to reflect actual clinical practice.

Patients on Symbicort had two options when their asthma symptoms increased: to increase the intake of reliever medication and progress on to oral steroids if an exacerbation developed; to increase the dose given by twice daily Symbicort in the same inhaler (due to the dose-responsiveness of the formoterol component). Both options for Symbicort were used in the SUND study to allow a review of the most appropriate treatment option.

Patients who had uncontrolled asthma should be brought under control by a period of fixed dosing and then, if appropriate, they could be given an asthma action plan to allow adjustable dosing with Symbicort. AstraZeneca noted that patients in the SUND study were given their previous inhaled steroids during the run-in period (2 weeks) and then randomised to one of three treatment arms for 7 months' therapy. For the adjustable treatment arm the first month was a fixed dose regimen to reflect actual clinical practice in bringing these patients under control.

In relation to the reference to the 40% reduction in severe exacerbations in claims 1 and 3 AstraZeneca noted that the complaint was focused on the time period of the study. Patients who had uncontrolled asthma should be brought under control by a period of fixed dosing and then, if they were treated with Symbicort, they could be given an asthma action plan to allow adjustable dosing (stepping up and down).

AstraZeneca submitted that the claims were made in relation to treatment arms that were wholly appropriate and reflective of clinical practice. It would be misrepresentative of the data if it was not to compare the whole of the treatment period the study took place over.

AstraZeneca did not accept that this was in breach of Clauses 7.2, 7.3 or 7.4.

AstraZeneca noted that the primary end-point of the SUND study was the odds of achieving a well-controlled asthma week. AstraZeneca submitted that it had not claimed superiority for the primary endpoint of control. The claim 'patients shown to be better controlled on adjustable dosing' was part of a sentence that specifically referred to severe exacerbation control. It could not be read as an individual phrase. A statement in the leavepiece that 'the primary endpoint (odds of a well-controlled asthma week) showed no significant difference between the treatment arms' appeared beside the chart of the reductions in exacerbations. The chart could not be viewed without seeing this statement.

AstraZeneca noted that the complaint questioned if the study was powered to examine difference in exacerbation rates. AstraZeneca submitted that the study was comparable in treatment arm size (around 200 patients) to the FACET study. The FACET study was a well-accepted study comparing exacerbation rates between differing doses of inhaled budesonide and inhaled budesonide plus formoterol in a similar patient population to the SUND study (Pauwels *et al* 1997). AstraZeneca submitted that as the treatment group sizes were similar it could be concluded that the SUND study was suitably powered for exacerbations.

The event rate for exacerbations in the SUND study was consistent with that shown in previous studies for adjustable dosing with Symbicort (Ställberg *et al*; Ind *et al* 2004). (These studies compared adjustable dosing and fixed dosing of Symbicort and included over 2,500 patients.)

AstraZeneca submitted that the manuscript of the SUND study (Aalbers *et al* 2004) provided statistical analysis for the 40% claim. A formal analysis of the total number of exacerbations over the full post-randomisation period (7 months) was performed by Poisson regression, a recognized analytical method for this type of data with the time in the study as an offset variable.

AstraZeneca noted that exacerbations were a secondary end-point of the SUND study and also

were a variable for the primary end-point: well-controlled asthma weeks. A well-controlled asthma week was defined as a week with: no night-time awakenings due to asthma; no exacerbations; no change in asthma treatment due to adverse events; AND at least two of the following: asthma symptom score of >1 on ≤ 2 days; ≤ 2 days of reliever medication use (maximum four occasions/week); morning PEF ≥ 80% of predicted normal value every day.

AstraZeneca submitted that the study was designed to compare two distinct paradigms of asthma management (adjustable versus fixed dosing). As such a global measure of asthma control was appropriate as a primary end-point. Currently the measure used in studies such as GOAL (Busse *et al* 2004) was well-controlled asthma weeks and it was appropriate to the same measure. However, this had its limitations in quantifying events that had a significant impact on patients' lives. Exacerbations had a larger clinical impact on patients and health professionals than other variables that completed a well-controlled asthma week such as the use of reliever medication on 5 occasions in a week.

- In the study, the definition of exacerbations was limited to clinically meaningful events – the need for oral steroid courses or emergency room visits/hospitalisation.
- For patients, these exacerbations would be a significant event and might result in time off work and impact to the patient and any carer.
- For doctors or practices, these asthma exacerbations would require medical intervention and place demands on healthcare resources.
- Given the above, a reduction of 40% fewer exacerbations was clinically significant.

AstraZeneca submitted that the claim did not mislead as to the clinical importance of this reduction. The claim was capable of substantiation as it clearly related to asthma exacerbations only and it was reflective of the available evidence. AstraZeneca submitted that it had also clearly stated there was no difference between treatment arms for the primary endpoint so as not to mislead. AstraZeneca therefore did not accept that this breached Clauses 7.2, 7.3 or 7.4.

In relation to the allegation of study bias AstraZeneca noted as above that the study was designed to compare dosing regimens most commonly used in clinical practice and was representative of actual clinical practice based on prescribing data and anecdotal evidence.

AstraZeneca submitted that Seretide was not licensed to be used in an adjustable dosage regimen and it was not aware of any evidence of this being recommended in the near future. A fixed dosage regimen for Seretide was therefore appropriate. Previous studies comparing adjustable dosing Symbicort with fixed dose Symbicort had shown similar results with regard to a reduction in asthma exacerbations in the adjustable dosing arm. AstraZeneca did not accept that the study design was biased, rather that it was designed to answer an important clinical question.

AstraZeneca submitted that in reviewing the points made above it had shown that the SUND study design was robust and was designed to be clinically relevant and to compare treatment regimens. This comparison of treatment regimens was reflected in the papers. AstraZeneca accepted that the study was designed to compare treatment regimens; Seretide was only licensed to be given in a fixed-dose regimen.

For the study to have been double-blind throughout would have required a highly complex design with at least four regular inhalers per treatment arm and would have raised concerns in interpretation of results.

AstraZeneca submitted that the manuscript provided statistical analysis for the 40% claim. A formal analysis of the total number of exacerbations of the full post-randomisation period (7 months) was performed by Poisson regression, a recognized analytical method for this type of data with the time in the study as an offset variable. In summary AstraZeneca considered that all the promotional activities related to the SUND study were accurate, balanced, fair, objective and unambiguous based on an up-to-date evaluation of all the evidence and reflected that evidence clearly.

The activities did not mislead as to the results of the study and were capable of substantiation.

AstraZeneca did not consider that the promotional activities relation to the SUND study were in breach of Clauses 7.2, 7.3 or 7.4.

In relation to the expert report submitted by GlaxoSmithKline, AstraZeneca stated that this was an evaluation of the SUND study, not a definitive clinical judgement; it listed personal opinion which did not constitute judgement on the claims made. The SUND study was published in a peer-reviewed journal, Current Medical Research and Opinions, and underwent the editorial scrutiny associated with acceptance by a peer-review journal. The authors of the paper clearly disclosed their relationship to AstraZeneca at the end of the article. As the evaluation made was a review of the manuscript and not a review of any promotional claims made from the manuscript, AstraZeneca provided a separate document by the lead author of the SUND study in reply to a GlaxoSmithKline expert.

AstraZeneca welcomed the opinion that 'the study design appeared reasonable in the main and the doses of drugs used seem appropriate'. AstraZeneca interpreted this as an endorsement of the study design in answering the clinical question the study aimed to address. AstraZeneca accepted there was no difference in the treatment arms for primary end-point and had stated this clearly on all promotional material relating to this study. AstraZeneca contested that hospitalisations were the only robust measure of the definition of an exacerbation.

AstraZeneca submitted that other clinical studies that had examined the occurrence of asthma exacerbations (FACET and EDICT) included the following as definitions of exacerbations: an increase in relief medication use; night time awakenings; deterioration of PEF; administration of additional inhaled steroids and administration of oral steroids.

The use of oral steroids in the community or through emergency room visits was a clinically important measure of patients' asthma control. Although managed mainly in the community, poor control was often referred to hospitals. Reducing exacerbations would reduce the cases referred to hospital, although not necessarily for immediate care. Only a small number of patients with serious asthma would require hospital admission for immediate care.

AstraZeneca accepted that patients in the adjustable arm would be likely to use less reliever medication if the increase in the dose of their primary medication resulted in a decrease in asthma symptoms. AstraZeneca did not believe this was a source of bias but a relevant variable to be measured to determine whether adjusting the dose of Symbicort helped to reduce asthma symptoms and so had an impact on patients.

AstraZeneca submitted that the objective of the study was to compare the efficacy of Symbicort Turbohaler, given as a fixed dose therapy or with an adjustable dosing regimen, with that of Seretide Diskus given as standard therapy in asthmatic adults and adolescents.

There were two Symbicort dosages available in the adjustable arm to reflect the needs of these patients for differing Symbicort dose. The analysis of both these groups together was a priori and was not done on a *post-hoc* basis.

AstraZeneca noted that the use of appropriate treatment group sizes to show a difference in exacerbation rate had been discussed above.

AstraZeneca submitted that it was implied that there were several differences in secondary outcomes that favoured fixed dose regimens, in fact there was only one. Evening PEF was the only variable that was in favour of either fixed dose regimen compared to adjustable dosing and it was in favour of both fixed dosage regimens. No other difference was in favour of the Seretide arm versus either of the Symbicort arms. Symbicort fixed dose and adjustable dosing was not compared in the analysis. A possible explanation of why evening PEF might be the only variable that went against the trend of the other results was given in the discussion section of the paper.

AstraZeneca submitted that the frequency of subjects reporting adverse events and serious adverse events was similar in all treatment groups. There were only two patients in the adjustable arm and one patient in the Symbicort fixed dose arm that had serious adverse events related to asthma, this accounted for less than 1% of each treatment arm.

AstraZeneca submitted that the discussion section of the paper discussed the limitation of the lack of blinding in the last 6-months of the study and the appropriateness of the choice of primary end-point. AstraZeneca had reviewed recent papers published in peer-reviewed journals on PubMed (a medical literature database), both with and without industry sponsorship. This review demonstrated that while it might be an ideal for the discussion to be critical, this was not always the case. AstraZeneca noted that the conflict of interest was declared clearly within the manuscript according to publishing standards.

In summary, AstraZeneca strongly believed that the SUND study answered an important clinical question; it was a well-designed study that reflected actual clinical practice; the promotional activity relating to this study was balanced, capable of substantiation by the data and was not misleading. AstraZeneca did not consider that it was in breach of Clauses 7.2, 7.3 and 7.4 in any of the areas discussed above.

PANEL RULING

The Panel noted that there were three claims at issue. The first two claims had been incorrectly cited by GlaxoSmithKline. The first headline claim read 'Symbicort ahead by 40% in severe exacerbation control:' followed immediately in smaller print by 'study confirms adjustable dosing is better than Seretide fixed dosing'. GlaxoSmithKline had incorrectly inserted the word 'Adjustable' at the beginning of the claim. The second claim read 'Symbicort superior to Seretide in severe exacerbation control: patients shown to be better controlled on adjustable Symbicort'. GlaxoSmithKline had incorrectly replaced the final word 'Symbicort' with 'dosing'. The final claim had been correctly cited by GlaxoSmithKline and read 'Patients on adjustable Symbicort benefited from 40% fewer severe exacerbations (p=0.018) compared with fixed dose Seretide according to a recent study'.

The Panel noted that the SUND study was designed to determine whether adjustable dosing with Symbicort had greater efficacy compared to fixed dose regimens with Seretide or Symbicort. The study comprised three treatment periods: run-in, double blind and a six month open extension during which patients received Seretide (one inhalation bid) or a fixed dose of Symbicort (two inhalations twice daily) or an adjustable dose of Symbicort (one or two inhalations bid, depending on the level of asthma control). The primary efficacy variable was the odds of having a well controlled asthma week during the post-randomisation period; a well controlled asthma week was defined as a week with no night-time awakenings due to asthma, no exacerbations and no change in asthma treatment due to adverse events plus at least two of the following: asthma symptom score of >1 on ≤ 2 days; ≤ 2 days of reliever medication use; morning PEF ≥ 80% of the predicted normal value every day. Exacerbations were defined as oral steroid treatment for ≥ 3 days, emergency room visits and/or hospitalisation. If oral steroids were used for more than 10 consecutive days the eleventh day was considered to be a second exacerbation. The study showed that the odds of achieving a well controlled asthma week over the whole treatment period were similar for fixed dose Seretide and adjustable dosed Symbicort. One fifth across all groups failed to achieve a single well controlled asthma week throughout the study period. Similarly no treatment differences were observed for total asthma control weeks.

Patients receiving adjustable dose Symbicort had fewer exacerbations than those receiving fixed dose Seretide (35 vs 59, p=0.018). The total rate of exacerbations over 7 months was 0.024/month and 0.041/month for Symbicort and Seretide respectively.

There was a statistically significant rate reduction of 39.7% (p=0.018) in favour of adjustable dose Symbicort. The results also showed that 57% of patients in the adjustable dose Symbicort group required no step-ups in treatment. Most patients who needed a temporary step-up regained control of their asthma in 7 days (67% of the step-up periods).

The study authors noted that adjustable dosing with Seretide was only possible by using a separate and additional inhaler to increase the dose of inhaled corticosteroid because the salmeterol dose response curve was limited.

The study authors explained that the definition of exacerbations was limited to clinically meaningful events. With increasing study duration Symbicort appeared to provide better asthma control: the difference in exacerbation rates in favour of Symbicort became more marked over time. However the use of well controlled asthma weeks alone only presented half the picture of a successful treatment outcome. The results highlighted the need for studying multiple measures of asthma control before drawing conclusions on the effectiveness of different regimens. Promptly increasing the dose of inhaled corticosteroid and long acting B2 agonists at the first sign of asthma worsening provided an early intervention strategy for the reduction of exacerbations.

The Panel noted that AstraZeneca had submitted a report from one of the study authors which noted that Seretide could achieve a similar dose adjustment to Symbicort but using three separate inhalers for the inhaled corticosteroid component which was beyond the scope of the study. In relation to the allegation that the study design was biased as fixed dose arms only had the option to use oral steroids if their asthma worsened the report explained that this was not the case; oral steroids were not used for self management but were only given by clinicians as a rescue medication if patients needed to consult their clinicians because of severe asthma attack. Symbicort patients who increased their maintenance treatment in response to an increased need for relief medication had less unscheduled clinic visits because of exacerbations that then resulted in less oral steroid use and emergency treatment.

The Panel noted AstraZeneca's explanation of the rationale for the design of the SUND study and further noted both parties' submission on the issue of bias.

The Panel noted the hypothesis of the SUND study was to determine whether adjustable dosing with a combination inhaler had greater efficacy compared with fixed dose regimens. The Panel noted that there was a difference regarding patients with inadequately controlled asthma. Under the study design patients on Symbicort could increase their dose of steroid (and consequently formoterol) whereas patients on Seretide could not increase their dose of steroid. The primary efficacy variable was the odds of having a well-controlled asthma week during the post-randomisation period. This, as noted above, was a composite measure. Total asthma control weeks were also analysed as was exacerbation data. Many of the asthma variables measured showed no statistically significant difference between adjustable dosed Symbicort and fixed dose Seretide. There was no difference between the two for well-controlled asthma weeks or total asthma control weeks, change in morning peak expiratory flow, night-time awakenings or daytime asthma symptom score. There was however a difference, in favour of adjustable dose Symbicort, with regard to the amount of reliever medication required ($p< 0.05$). There was also a 40% reduction in the number of severe exacerbations which occurred in those taking adjustable dose Symbicort compared to those taking fixed dose Seretide (p=0.018). The authors stated that this treatment difference related to a reduction of 20 severe exacerbations per 100 patients/year (numbers needed to treat – 4.9).

The Panel noted that the leavepiece at issue concentrated wholly on the data from the SUND study with regard to severe exacerbations. This was only one aspect of asthma control. The only reference in the leavepiece to the primary endpoint of the study was a statement at the bottom of a bar chart, which took up the whole of page 3, that 'The primary endpoint (odds of a well-controlled asthma week) showed no significant difference between the treatment arms'. The Panel considered that by focussing solely on exacerbation data the leavepiece did not give a balanced and fair overview of the comparison of adjustable dose Symbicort and fixed dose Seretide. In the Panel's view some readers might be misled and assume that in all aspects of asthma control Symbicort was better than Seretide which was not the case. This impression was compounded by a caption to a photograph on the back page which stated 'She missed the sales last year – now, after gaining control with adjustable Symbicort, she can enjoy shopping without symptoms'. The Panel thus concluded that given the context in which they appeared the claims 'Symbicort ahead by 40% in severe exacerbation control: study confirms adjustable dosing is better than Seretide fixed dosing', 'Symbicort superior to Seretide in severe exacerbation control: patients shown to be better controlled on adjustable Symbicort' and 'Patients on adjustable Symbicort benefited from 40% fewer severe exacerbations (p=0.018) compared with fixed dose Seretide according to a recent study' were not a fair reflection of the outcome of the SUND study. The claims were misleading in this regard and thus could not be substantiated. Breaches of Clauses 7.2, 7.3 and 7.4 of the Code were ruled.

Complaint received **20 April 2004**

Case completed **21 July 2004**

CASE AUTH/1580/4/04

HEAD OF PRIMARY CARE TRUST PRESCRIBING SUPPORT UNIT v GLAXOSMITHKLINE

Avandia and Avandamet journal advertisement

The head of a primary care trust prescribing support unit complained about a claim that using rosiglitazone could also help lower blood pressure which appeared in a journal advertisement for Avandia (rosiglitazone) and Avandamet (rosiglitazone/metformin) issued by GlaxoSmithKline.

The complainant could find no reference to blood pressure lowering in the Avandia summary of product characteristics (SPC), although side effects likely to cause increased blood pressure were described. The complainant questioned whether this supposedly additional benefit from rosiglitazone could be advertised in this manner.

The Panel noted that the advertisement was headed 'Confront the new challenges for Type 2 diabetes' and referred to rosiglitazone available as Avandia and, in combination with metformin, as Avandamet. Both products were for the treatment of Type 2 diabetes. Avandia could be used as monotherapy particularly in overweight patients inadequately controlled by diet and exercise and for whom metformin was inappropriate. It could also be used in combination treatment in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea. Avandamet was indicated particularly for the treatment of overweight patients who were unable to achieve sufficient glycaemic control at their maximally tolerated dose of metformin alone.

The introductory paragraph of the advertisement stated that managing Type 2 diabetes was no longer just about glycaemic control and that this was why the General Medical Services (GMS) contract focussed 'on both lasting glycaemic control and reductions in blood pressure'. The remainder of the paragraph discussed tight glycaemic control and its association with fewer microvascular complications and tight blood pressure control and its association with fewer major cardiovascular events.

The following paragraph explained that rosiglitazone could help meet both blood glucose and blood pressure GMS targets by targeting insulin resistance, a root cause of Type 2 diabetes. A subsequent paragraph began 'By targeting insulin resistance, rosiglitazone also helps to achieve blood pressure targets …' and discussed studies which had consistently shown that rosiglitazone helped to significantly lower blood pressure. The effect of rosiglitazone on blood pressure was compared to that of sulphonylureas and it was further noted that the 'UKPDS [UK Prospective Diabetes Study] found that sulphonylureas had no significant effect on cardiovascular outcomes after a mean treatment period of 10 years'. The final paragraph referred to Avandia and Avandamet. The claims 'You really want to hit targets year after year' and 'Using the right oral antidiabetic agent can also help lower blood pressure' appeared in highlighted circles.

The Panel noted that there was evidence showing a beneficial effect of Avandia on blood pressure in Type 2 diabetics. Whilst it was not necessarily unacceptable to refer to such a benefit in promotional material such references should comply with the Code and could only be made within the context of treating patients for the product's licensed indications. The Panel considered that the balance of the advertisement was such that the reduction of blood pressure as a benefit of using Avandia or Avandamet had been given undue emphasis; it had not been placed sufficiently within the context of the licensed indications. The advertisement implied that Avandia and Avandamet were indicated for blood pressure reduction and that was not so; the advertisement was misleading and inconsistent with the marketing authorizations in this regard. Breaches of the Code were ruled.

The head of the prescribing support unit of a primary care trust (PCT) complained about a journal advertisement (AVM/FPA/04/11822/1) for Avandia (rosiglitazone) and Avandamet (rosiglitazone/metformin) issued by GlaxoSmithKline UK Limited.

COMPLAINT

The complainant was particularly concerned about the claim that using rosiglitazone could also help lower blood pressure. The complainant could find no reference to this action in the summary of product characteristics (SPC), although side effects (weight gain, fluid retention and cardiac failure) likely to cause increased blood pressure were described.

The complainant questioned whether this supposedly additional benefit from rosiglitazone could be advertised in this manner.

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

RESPONSE

GlaxoSmithKline noted that the complainant appeared to make two separate allegations: firstly, that, irrespective of any evidence, it was not permitted under the Code to make claims concerning the effects of Avandia on blood pressure, inasmuch as such effects were not mentioned in the SPC; and, secondly, that the claims made might not accurately represent a true benefit or clinical effect of the product.

GlaxoSmithKline noted Clause 3.2 that the promotion of a medicine 'must not be inconsistent' with the particulars listed in its SPC. GlaxoSmithKline submitted that drawing the attention of prescribers to highly relevant additional pharmacodynamic properties of a product not specifically mentioned in its SPC did not contravene this provision. The final

paragraph of the advertisement in question clearly stated the groups of patients for whom Avandia was indicated, and these were in accordance with the SPC. GlaxoSmithKline therefore did not consider that the advertisement sought to promote Avandia outwith the terms of its marketing authorization.

GlaxoSmithKline noted that by its nature, an SPC could not act as a repository of all clinical information pertinent to a medicine. Indeed, the 'Guideline on Summary of Product Characteristics' issued by the European Commission stated that, for the 'Pharmacodynamic properties' section of an SPC, 'In general, no information is expected'. It would evidently be impracticable to apply for an SPC amendment on each occasion that a new piece of evidence about a product became available. To interpret Clause 3.2 in the highly restrictive sense apparently advocated by the complainant would have a deleterious effect on education and scientific information relating to medicines; and would deprive health professionals of easy access to research findings that could potentially be of great benefit to themselves and to their patients.

GlaxoSmithKline submitted that in this respect, the importance of vigorously addressing raised blood pressure in Type 2 diabetic patients was indisputable. The United Kingdom Prospective Diabetes Study (UKPDS), the only major prospective outcome study in this condition conducted to date – demonstrated that tight blood pressure control was the single most important factor in reducing the incidence of macrovascular complications, including myocardial infarction, stroke, and sudden death. There was a 34% reduction in adverse cardiovascular outcomes in the tight blood pressure control group compared with the 'standard' control group. However, the study also demonstrated the difficulty of achieving optimum control: nearly 45% of patients in the tight control group failed to maintain their target blood pressure; and 60% of hypertensive patients needed two or more antihypertensive agents, and 29% three or more agents, to maintain adequate control. In this context, the ancillary antihypertensive effects of an antidiabetic agent such as Avandia were highly relevant, particularly given that the main alternatives, the sulphonylureas, had no consistent effect on blood pressure.

GlaxoSmithKline noted that the Medicines and Healthcare products Regulatory Agency (MHRA) had recently completed a review of promotion of the glitazones. GlaxoSmithKline provided a copy of a recent letter from the MHRA which stated that 'The evidence shows that glitazones may have a secondary effect on other parameters such as…blood pressure, in diabetic patients…' and went on to allow promotion of such secondary effects, provided that they were not given undue prominence relative to the antihyperglycaemic effects, and that it was made clear that they resulted from the primary mode of action of the glitazones, ie improving insulin resistance. Both of these provisos were met in the advertisement in question. In reaching these conclusions the MHRA implicitly acknowledged that promotion of the effects of glitazones on blood pressure was consistent with the marketing authorization for these agents and, explicitly, that the evidence base was sufficient to justify such promotion.

GlaxoSmithKline submitted that to assess whether the advertisement was in breach of Clause 7.2 of the Code, it was necessary to examine this evidence base. Notwithstanding the complainant citing several uncommon side-effects of glitazones, there was a large, consistent and growing body of evidence that Avandia had clinically and statistically significant effects in lowering blood pressure. These effects had been noted in practically all trials with Avandia conducted to date in which blood pressure had been examined. GlaxoSmithKline provided a table summarising blood pressure changes seen with Avandia in eleven clinical and observational trials: eight in diabetics (n > 7,500), and three in non-diabetics (only the trials in diabetics were referenced in the advertisement). GlaxoSmithKline also presented a bar chart setting out the blood pressure drops seen in these studies. GlaxoSmithKline submitted that despite variations in study methodology, duration and design, the results were clearly completely consistent. Without exception, there was a statistically significant reduction in both systolic (3.5 – 20mmHg) and diastolic (2.7-17mmHg) blood pressure with Avandia.

GlaxoSmithKline submitted that the reality and significance of the blood pressure effects of glitazones had been attested to by several independent experts in clinical reviews of the cardiovascular effects of glitazones. Bakris *et al* (2003) stated 'Glucose control with traditional oral hypoglycemic agents, such as sulphonylureas, has failed to show any reduction in blood pressure. Insulin sensitization with [glitazones], however, has demonstrated a reduction of elevated blood pressure…'. Likewise, Greenberg *et al* (2003), stated '[Glitazone] therapy has significant effects on the traditional elements of the metabolic syndrome, including dyslipidemia and hypertension' and 'The [glitazones] also reduce elevated blood pressure in patients with type 2 diabetes, and rosiglitazone has been shown to lower the expression and secretion of the angiotensin II precursor, angiotensinogen'. Viberti *et al* (2003) stated 'An important component of the [metabolic syndrome], hypertension is linked with insulin resistance, hence it has been proposed that agents that reduce insulin resistance such as the [glitazones] may have beneficial effects on blood pressure in patients with type 2 diabetes. Preliminary evidence indicates that this is the case, and small but significant decreases in blood pressure have been reported in patients treated with rosiglitazone'. GlaxoSmithKline noted that this report was written prior to publication of several of the eleven clinical and observational trials on Avandia in which blood pressure had been examined and which were referred to above, in which much larger drops were observed. Finally, as noted above, the MHRA had recognised that the evidence on the blood pressure effects of glitazones was sufficient to justify promotional claims.

In summary, GlaxoSmithKline maintained that the advertisement in question was not inconsistent with the Avandia SPC and that it was permissible to make promotional claims relating to the secondary

pharmacodynamic effects of a medicine, provided that the effects were relevant (which they most certainly were in this case) and were supported by the balance of the evidence. In the case of the action of Avandia on blood pressure, the existing evidence was overwhelmingly in favour of a clinically and statistically significant beneficial effect. This was endorsed by numerous independent experts. The MHRA had also concluded that the evidence base was sufficient to justify promotional claims and (implicitly) that such claims might be made, subject to certain conditions, within the terms of the existing marketing authorization for Avandia.

As such, GlaxoSmithKline did not consider that the advertisement was in breach of Clauses 3.2 or 7.2 of the Code.

PANEL RULING

The Panel noted that the advertisement was headed 'Confront the new challenges for Type 2 diabetes' and referred to rosiglitazone available as Avandia and, in combination with metformin, as Avandamet. The Panel noted that Avandia was indicated as oral monotherapy treatment of Type 2 diabetics particularly in overweight patients inadequately controlled by diet and exercise and for whom metformin was inappropriate because of contraindications or intolerance. Avandia was also indicated in oral combination treatment in patients 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 who showed intolerance to metformin or for whom metformin was contraindicated. Avandamet was indicated for the treatment of Type 2 diabetics, particularly overweight patients, who were unable to achieve sufficient glycaemic control at their maximally tolerated dose of metformin alone.

The Panel noted that the introductory paragraph of the advertisement stated that managing Type 2 diabetes was no longer just about glycaemic control and that this was why the GMS contract focussed 'on both lasting glycaemic control and reductions in blood pressure'. The remainder of the paragraph discussed tight glycaemic control and its association with fewer microvascular complications and tight blood pressure control and its association with fewer major cardiovascular events.

The following paragraph explained that rosiglitazone could help meet both blood glucose and blood pressure GMS targets by targeting insulin resistance, a root cause of Type 2 diabetes. Reference was made to hitting 'targets year after year' within the context of rosiglitazone's 'proven lasting effectiveness'. A subsequent paragraph began 'By targeting insulin resistance, rosiglitazone also helps to achieve blood pressure targets …' and discussed studies which had consistently shown that rosiglitazone helped to significantly lower blood pressure. The effect of rosiglitazone on blood pressure was compared to that of sulphonylureas and it was further noted that the 'UKPDS found that sulphonylureas had no significant effect on cardiovascular outcomes after a mean treatment period of 10 years'. The final paragraph referred to Avandia and Avandamet. The claims 'You really want to hit targets year after year' and 'Using the right oral antidiabetic agent can also help lower blood pressure' appeared in highlighted circles.

The Panel considered there was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition.

The Panel noted that there was evidence showing a beneficial effect of Avandia on blood pressure in Type 2 diabetics. Whilst it was not necessarily unacceptable to refer to such a benefit in promotional material such references should comply with the Code and could only be made within the context of treating patients for the product's licensed indications. The Panel considered that the balance of the advertisement was such that the reduction of blood pressure as a benefit of using Avandia or Avandamet had been given undue emphasis. The advertisement did not place reduction in blood pressure sufficiently within the context of the licensed indications for the products. The advertisement gave the impression that Avandia and Avandamet were indicated for blood pressure reduction and that was not so; the advertisement was misleading and inconsistent with the marketing authorizations in this regard. Breaches of Clauses 3.2 and 7.2 were ruled.

Complaint received **20 April 2004**

Case completed **23 June 2004**

NOVO NORDISK v AVENTIS PHARMA

Lantus booklets

Novo Nordisk complained about the promotion of Lantus (insulin glargine) by Aventis Pharma. Lantus was indicated for the treatment of diabetes mellitus where treatment with insulin was required. It should be administered once daily at any time but at the same time each day. The materials at issue, a four page booklet and a six page booklet, included as a heading on the front covers 'For Type 1 and Type 2 diabetes, treat to A1c target with 24-hour control'. 'Treat to A1c with 24-hour control' also appeared as a strapline beneath the product logo in both booklets. Novo Nordisk considered that the claim for '24-hour control' was not supported by sufficient clinical data. Novo Nordisk supplied a range of insulins.

Novo Nordisk noted that the Medicines and Healthcare products Regulatory Agency had recently stated that 'claims for 24-hour relief need to be supported by *clinical effectiveness* over a full 24-hour period' (emphasis added by Novo Nordisk). In Novo Nordisk's view the claim of '24-hour control' was a claim of clinical effectiveness and needed to be supported by clinical data. However, data cited in support of the claim was derived from a pharmacodynamic study (Lepore *et al* 2000). Novo Nordisk did not consider that such data could be extrapolated to support a claim of '24-hour control', which was a clinical effectiveness claim. In intercompany correspondence Aventis had agreed that Lepore *et al* was an 'artificial situation', and that 'repeated dosing is required for adequate clinical management of diabetes'. Aventis referred to Fanelli *et al* (2002) which was a pharmacodynamic study and was not referred to in either booklet.

Novo Nordisk was also concerned about over-claiming from the evidence. Aventis had stated that plasma insulin levels following injection of glargine plateaued at a concentration of 18.9 +/- 0.3µU between 3 and 24 hours. Novo Nordisk noted that plasma insulin levels did not necessarily translate into pharmacodynamic activity (ie glucose lowering effect).

Furthermore, Aventis had stated that 'glucose infusion rate following injection of glargine stabilised at 3 hrs and was nearly constant to 24 hours', and 'plasma glucose following injection of glargine remained at the target value until 15 hrs'. However Lepore *et al* showed that duration of action of the 0.3U/kg of subcutaneous injection of Lantus was 20.5 +/- 3.7 hours. In Novo Nordisk's view this was over-claiming the duration of action of insulin glargine.

Novo Nordisk alleged that the booklets were misleading and could not be supported by the cited papers.

The Panel noted that Lepore *et al* compared the pharmacokinetics and pharmacodynamics of one dose of Lantus with other insulins in 20 patients. Lepore *et al* concluded that glargine was a peakless insulin which lasted nearly 24 hours.

Fanelli *et al* examined the effect of a daily dose of Lantus for a week on 20 patients and concluded that after 7 days of administration onset of action was earlier, the duration of action closer to 24 hours, the action profile flatter, the insulin action greater and inter-individual variability lower as compared to its first injection. The duration of action for day 1 of the study was 20.5 ± 3.7 hours and for day 7 was 23.2 + 1.3 hours. There was a statistically significantly different result for day 7 compared to day 1 with regard to onset of action, end of action and duration of action.

The Panel noted that the Lantus summary of product characteristics (SPC) stated that it should be administered once a day. The Panel also noted the results from Lepore *et al* and Fanelli *et al*. The Panel considered that the reference to 24-hour control in the claim at issue 'Treat to A1c target with 24-hour control' was not unreasonable. Data had been provided to support the claim which the Panel considered was not misleading as alleged. The Panel thus ruled no breaches of the Code.

Novo Nordisk Limited complained about the promotion of Lantus (insulin glargine) by Aventis Pharma Ltd. The materials at issue were a four page booklet (ref LAN2780403) and a six page booklet (ref LAN3420703). The front covers of both were headed 'For Type 1 and Type 2 diabetes, treat to A1c target with 24-hour control'. 'Treat to A1c with 24-hour control' also appeared as a strapline beneath the product logo in both booklets.

Lantus was indicated for the treatment of diabetes mellitus where treatment with insulin was required. It should be administered once daily at any time but at the same time each day.

Novo Nordisk supplied a range of insulins.

COMPLAINT

Novo Nordisk considered that the claim for '24-hour control' was not supported by sufficient clinical data. Breaches of Clauses 7.2 and 7.4 of the Code were alleged.

Novo Nordisk noted that a recent announcement from the Medicines and Healthcare products Regulatory Agency (MHRA) stated that 'claims for 24-hour relief need to be supported by *clinical effectiveness* over a full 24-hour period' (emphasis added by Novo Nordisk). In Novo Nordisk's view the claim of '24-hour control' was a claim of clinical effectiveness and needed to be supported by data from phase 2 to 4 clinical trials. However, data cited in support of the claim was derived from a pharmacodynamic study (Lepore *et al* 2000). Novo Nordisk did not consider that such data could be extrapolated to support a claim of '24-hour control', which was essentially a clinical effectiveness claim.

In intercompany correspondence Aventis agreed that Lepore *et al* was an 'artificial situation', and that 'repeated dosing is required for adequate clinical management of diabetes'. Aventis referred to Fanelli *et al* (2002) which was a pharmacodynamic study and was not referred to in either booklet.

Novo Nordisk was also concerned about over-claiming from the evidence. Aventis had stated in intercompany correspondence that plasma insulin levels following injection of glargine plateaued at a concentration of 18.9 +/- 0.3µU between 3 and 24 hours. Novo Nordisk noted that plasma insulin levels did not necessarily translate into pharmacodynamic activity (ie glucose lowering effect).

Furthermore, Aventis had stated that 'glucose infusion rate following injection of glargine stabilised at 3 hrs and was *nearly constant* to 24 hours', and 'plasma glucose following injection of glargine remained at the target value until 15 hrs'. However a closer scrutiny of Lepore *et al* revealed that duration of action of the 0.3U/kg of subcutaneous injection of Lantus was 20.5 +/- 3.7 hours. In Novo Nordisk's view this was over-claiming the duration of action of insulin glargine.

Novo Nordisk therefore concluded that the booklets were misleading and could not be supported by the cited papers. Breaches of Clauses 7.2 and 7.4 of the Code were alleged.

RESPONSE

In relation to the claim 'Treat to A1c target with 24-hour control' Aventis noted the MHRA advice stated: 'For 24 hour relief, data must show clinical effect that over the 24 hour period' and 'Evidence of blood levels alone is unlikely to be sufficient to support a claim'. In this context Aventis further noted that the clinical effect of all insulins lay in their ability to lower blood glucose. Therefore Aventis considered that to make a claim of 24-hour control for Lantus, fulfilling the criteria that the MHRA had advised, it was necessary to show that it exerted a clinically relevant glucose lowering effect over a 24-hour period. The established gold standard method of showing the duration of action of any insulin accurately was an isoglycaemic clamp study that measured both the pharmacokinetic and pharmacodynamic properties of the insulin in question. Novo Nordisk was wrong to consider that data from such studies was inappropriate. Moreover, the MHRA advice did not make reference to 'clinical effectiveness', nor did it mandate that data from phase 2 to 4 clinical trials, was required in order to make a promotional claim, as stated by Novo Nordisk.

Lepore *et al* reported the pharmacokinetic and pharmacodynamic response in the 24-hours following a single subcutaneous injection 0.3U/kg of Lantus in twenty subjects with Type 1 diabetes (in comparison to isophane insulin, ultralente insulin and a continuous subcutaneous infusion of insulin lispro). The study concluded that the duration of action of insulin glargine, defined as the length of time between the onset of action (the time after injection that the rate of intravenous insulin decreased by 50% compared to the pre-injection time period) and the end of action (the time at which plasma glucose in each subject consistently increased above 150mg/dl) was 20.5 +/- 3.7hrs. Moreover the authors reflected that the duration of action was underestimated using the above definition of end of action, as in a Type 1 subject who had an absolute insulin deficiency, a plasma glucose above 150mg/dl reflected that the insulin was continuing to exert activity (the plasma glucose would be considerably higher if no insulin activity was present). The study also noted that in 6 out of 20 subjects, the end of action was underestimated because when a study terminated at the 24-hour point, plasma glucose concentrations remained below 150mg/dl in those subjects. Plasma insulin levels following the injection of insulin glargine increased to a plateau concentration of 18.9 +/- 0.3 µU/ml between 3 and 24-hours (study termination).

Fanelli *et al* reported the pharmacodynamic response following the subcutaneous administration of 0.3U/kg Lantus in twenty subjects with Type 1 diabetes. This differed from Lepore *et al* as subjects were studied on two occasions, once following the first injection of Lantus and seven days later, having received a once daily injection of Lantus on each of the intervening days. Lantus levels reached steady state in an individual after 2 to 4 days. Therefore the isoglycaemic clamp study on the seventh day showed a duration of action of Lantus at steady state. This study reflected the real-life situation where a diabetic required repeated insulin doses each day to manage their disease. The results showed that the duration of action of insulin glargine on day 7 (using the same definitions as in the Lepore study *et al*) was 23.9 +/- 1hrs.

In addition, the glucose continued to be infused up to 32 hours after study start, which was a reflection that Lantus continued to exert a metabolic effect up to that point.

In conclusion, Lepore *et al* showed that following a first single injection of Lantus of 0.3U/kg, the duration of action using pre-defined parameters was 20.5hrs +/- 3.7hrs. However at the end of the study, clear indication of continued Lantus activity was present (plasma insulin levels and controlled plasma glucose levels in 16 subjects) though this could not be further quantified as the study terminated at this point. Fanelli *et al* developed the evidence further, showing that when Lantus had reached steady state, its duration of action using the same definitions was 23.9 +/- 1.0hrs, with clear evidence of continued metabolic action well beyond the 24-hour point. Aventis submitted that these two studies clearly demonstrated that Lantus showed clinical effect over the 24-hour period and were sufficient to substantiate the claim in question.

In its complaint Novo Nordisk alleged that Aventis had 'over-claimed' with reference to Lepore *et al*; however no mention was made of the data from Fanelli *et al*. Aventis noted that when asked to substantiate the claim, it clearly made reference to both studies and that both were used as substantiation. The suggestion of 'over claiming' on Lepore *et al*, was therefore incorrect.

The isoglycaemic clamp studies presented above were the gold standard technique for establishing the pharmacokinetics and pharmacodynamics of Lantus. Randomised controlled clinical studies also reported pharmacodynamic end points. However, the disadvantage of such studies was that more than insulin was usually required to control blood glucose

in clinical practice. For example, a 'basal bolus' regimen included a basal insulin to provide a background level of insulin and a short acting insulin or 'bolus' to provide extra insulin to lower the raised blood glucose that occurred after each meal. The results thus reflected the pharmacodynamics of the combined regime of insulin and precise assessment of the duration of action of each specific insulin was difficult to determine. However, despite this caveat, clinical studies confirmed the findings from the isoglycaemic clamp studies presented above regarding the duration of action of Lantus.

Hamann *et al* (2003) reported a clinical study in which 378 patients with Type 1 diabetes were treated with once daily Lantus together with insulin lispro given at meal-times, over a 24-week period. Patients were randomised into three groups, with each group receiving insulin glargine either at breakfast, dinner or bedtime. The glucodynamic profile of each patient was examined at the end of each study using 8 self-monitored blood glucose measurements over a 24 hour period. The authors reported that 'the 24 hour blood glucose profiles were comparable, regardless of the time of insulin glargine administration and confirmed the flat, reproducible glucodynamic profile following once-daily administration of insulin glargine'.

In summary, isoglycaemic clamp studies were the appropriate method to show the duration of clinical effect of an insulin. The data presented from Lepore *et al* and Fanelli *et al* showed that Lantus exerted a clinical effect in lowering blood glucose that extended to 24-hours and beyond. These findings were confirmed by clinical data from Hamann *et al* when insulin glargine was combined with insulin lispro in a basal bolus regimen for the practical treatment of diabetes. In addition Lantus had been approved for once daily dosing by the European Medicines Evaluation Agency following consideration of just such data; this was reflected in the Lantus summary of product characteristics (SPC). Therefore Aventis was confident that the claim in question had been clearly substantiated and was not in breach of Clauses 7.2 and 7.4 of the Code.

PANEL RULING

The Panel noted that Lepore *et al* compared the pharmacokinetics and pharmacodynamics of one dose of Lantus with other insulins in 20 patients. Lepore *et al* concluded that glargine was a peakless insulin which lasted nearly 24 hours.

Fanelli *et al* examined the effect of a daily dose of Lantus for a week on 20 patients. Fanelli *et al* which was presented as an abstract concluded that after 7 days of administration onset of action was earlier, the duration of action closer to 24 hours, the action profile flatter, the insulin action greater and inter-individual variability lower as compared to its first injection. The duration of action for day 1 of the study was 20.5 ± 3.7 hours and for day 7 was 23.2 ± 1.3 hours. There was a statistically significantly different result for day 7 compared to day 1 with regard to onset of action, end of action and duration of action.

The Panel noted that the Lantus SPC stated that it should be administered once a day. The Panel also noted the results from Lepore *et al* and Fanelli *et al*. The Panel considered that the reference to 24-hour control in the claim at issue 'Treat to A1c target with 24-hour control' was not unreasonable. Data had been provided to support the claim which the Panel considered was not misleading as alleged. The Panel thus ruled no breach of Clauses 7.2 and 7.4 of the Code.

Complaint received **29 April 2004**

Case completed **13 July 2004**

DIABETES SPECIALIST NURSE v AVENTIS PHARMA

Alleged promotion of Lantus to diabetes group

A diabetes specialist nurse complained about a poster advertising a meeting at which it was stated that a representative from Aventis Pharma would give a talk to a local group of Diabetes UK on Lantus insulin (insulin glargine).

The complainant understood that the Code prohibited the advertising of prescription only medicines to the public and was concerned that the representative was prepared to advertise her company's insulin to a group of patients. The complainant firmly believed that insulin treatment for patients should be on an individual basis and whilst Lantus was a very useful insulin, it was not appropriate for all.

The Panel noted that the poster announced that a named representative from Aventis would be giving a talk on Lantus insulin on Wednesday, 19 May, at 7pm. All were welcome. The Diabetes UK logo appeared in the top right hand corner and further details about the charity appeared at the bottom.

The Panel was concerned that the representative was going to talk to members of the public at a local branch meeting of Diabetes UK. The main role of a representative was to promote medicines. The Panel noted that the chair of the local Diabetes UK group had mistakenly assumed that the representative was going to talk about Lantus. Whilst it was not necessarily unacceptable for representatives to talk to the public the company should exercise extreme caution when instructing them on such activity.

The Panel noted Aventis' submission that during a routine sales call in 2003 the representative met a person from Diabetes UK who invited her to give a talk at its local meeting on 19 May 2004. The content of the talk was discussed. The representative believed she had made it clear that she was not permitted to discuss any diabetes product made by Aventis. There had been no further contact between the parties in the intervening months. The representative had been unaware of the title of the talk and the steps taken by Diabetes UK to advertise it.

The Panel noted that there had been no contact between the representative and Diabetes UK since 18 June 2003, when the meeting was arranged, until shortly after 5 May 2004 when Aventis was notified of the complaint, two weeks before the meeting was scheduled to take place. The Panel noted Aventis' conclusion that this matter arose as a direct result of the absence of communication between the representative and Diabetes UK during this time. The Panel considered that when meetings were arranged the company ought to ensure, at the outset, that the respective roles and responsibilities of all parties involved were discussed and agreed and that third parties were aware of the relevant requirements of the Code.

The Panel noted the company's submission that the representative was going to talk about the range of non-promotional materials produced by Aventis for patients. The Panel ruled no breach of the Code. The Panel was concerned about the overall arrangements for the meeting, the role of the representative and the impression given. The Panel noted Aventis' submission that it had nothing to do with the poster. On balance, however, given the particular circumstances of this case the Panel did not consider that either the representative or the company had failed to maintain a high standard of ethical conduct. No breach of the Code was ruled. Nor did the Panel consider that the company had brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

A diabetes specialist nurse complained about a poster advertising a meeting at which it was stated that a representative from Aventis Pharma Ltd would give a talk to a local group of Diabetes UK on Lantus insulin (insulin glargine).

COMPLAINT

The complainant understood that Clause 20 of the Code prohibited the advertising of prescription only medicines to the public and was concerned that the representative was prepared to advertise her company's insulin to a group of patients. The complainant firmly believed that insulin treatment for patients should be on an individual basis and whilst Lantus was a very useful insulin, it was not appropriate for all.

When writing to Aventis the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2 and 20.1 of the Code.

RESPONSE

Aventis stated that during a routine sales call with a hospital diabetes specialist nurse on 18 June 2003, the Aventis representative was introduced to a representative of a local branch of Diabetes UK (a charity for people with diabetes). The representative was asked if she would attend one of the group's forthcoming meetings, to which she agreed. She planned to talk at the meeting about the range of non-promotional patient materials that Aventis produced and supplied for diabetics and their carers (titles in the range included, 'Understanding type 1 diabetes', 'Understanding type 2 diabetes' and 'What is a hypo?'). Though the content of the talk was discussed and the date of 19 May 2004 set, no firm title for the talk was decided. The representative believed that she had made it clear that she was not permitted to discuss any products made by Aventis for the treatment of diabetes.

The representative had not been in contact with the local Diabetes UK group during the intervening months and the first knowledge that she had of the title of the talk and the arrangements that Diabetes UK had made to advertise it, was when Aventis received notice of this complaint. It went without saying that as an experienced representative she would neither have undertaken, not agreed to undertake, any activity that could be interpreted as promoting Lantus, or any other products manufactured by Aventis, to patients.

Upon receipt of the complaint, Aventis contacted the chair of the local Diabetes UK group. She corroborated the above account of events and had written to the Authority to clarify matters.

Aventis explained that the meeting was to be held at the initiative of the local Diabetes UK group and that the representative had not prepared a presentation. Aventis was not aware of the exact list of invitees but assumed that it would have been the members of Diabetes UK affiliated to the local branch. Aventis was not aware where the poster was displayed.

In summary, Diabetes UK had set the title of the talk and produced and posted the posters without the knowledge of Aventis. The representative had no intention of presenting information about specific products that Aventis manufactured for the treatment of diabetes and was well aware of the constraints of the Code in this regard. Aventis concluded that this unfortunate episode came about as a direct result of the absence of communication between the representative and Diabetes UK over the intervening ten months. This was most certainly not a meeting that was planned by Aventis to promote Lantus direct to members of the general public. As a result Aventis did not consider this episode represented a breach of the Code on the part of Aventis.

* * * * *

The chair of the local Diabetes UK voluntary group wrote to the Authority and explained that the talk, which had been verbally and informally arranged in June 2003, was erroneously entitled 'A talk on the subject of Lantus Insulin'. This title had been mistakenly assumed to be correct without proper consultation or agreement with the representative who was completely unaware of it until publication – a communication failure.

The group was very concerned that this unfortunate incident had occurred and for any distress caused. There was never any intention to contravene the Code. The group could only apologise for what was a genuine and innocent mistake, and one that that it would endeavour to avoid in future. The subject of the talk had been cancelled and all posters were immediately requested to be removed.

PANEL RULING

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.

The Panel noted that the poster at issue announced that a named representative from Aventis would be giving a talk on Lantus insulin on Wednesday, 19 May, at 7pm. All were welcome. The Diabetes UK logo appeared in the top right hand corner and further details about the charity appeared at the bottom.

The Panel was concerned that the representative was going to give a talk to members of the public at a local branch meeting of Diabetes UK. The main role of a representative was to promote medicines. The Panel noted that the chair of the local Diabetes UK group had mistakenly assumed that the representative was going to give a talk about Lantus. Whilst it was not necessarily unacceptable for representatives to talk to the public, the company should exercise extreme caution when instructing representatives on such activity and take great care to ensure that all of the arrangements complied with the Code, especially the provisions of Clause 20.

The Panel noted Aventis' submission that during a routine sales call last year the representative was introduced to a person from Diabetes UK who invited her to give a talk at its local meeting on 19 May. The content of the talk was discussed. The representative believed she had made it clear that she was not permitted to discuss any diabetes product made by Aventis. There had been no further contact between the parties in the intervening months. The representative had been unaware of the title of the talk and the steps taken by Diabetes UK to advertise it.

The Panel was concerned about the overall arrangements for the meeting. The Panel noted that there had been no contact between the representative and Diabetes UK since 18 June 2003, when the meeting was arranged until shortly after 5 May 2004 when Aventis was notified of the complaint, two weeks before the meeting was scheduled to take place on 19 May. The Panel noted Aventis' conclusion that this matter arose as a direct result of the absence of communication between the representative and Diabetes UK during this time. The Panel considered that when meetings were arranged the company ought to ensure, at the outset, that the respective roles and responsibilities of all parties involved were discussed and agreed and that third parties were aware of the relevant requirements of the Code so that their actions would not render companies in breach of the Code. When patients were involved the Panel considered that it was especially important that these arrangements were recorded between the parties.

The Panel noted the company's submission about the content of the presentation; the representative was going to talk about the range of non-promotional materials produced by Aventis for patients. The Panel ruled no breach of Clause 20.1 of the Code. The Panel was concerned about the overall arrangements for the meeting, the role of the representative and the impression given. The Panel noted Aventis' submission that it had nothing to do with the poster. On balance, however, given the particular circumstances of this case the Panel did not consider that the representative had failed to maintain a high standard of ethical conduct. No breach of Clause 15.2 was ruled. Nor did the Panel consider that these particular circumstances meant that the company had failed to maintain high standards or brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clauses 9.1 and 2 was ruled.

Complaint received **4 May 2004**

Case completed **5 July 2004**

CASES AUTH/1588/5/04 and AUTH/1589/5/04

PRIMARY CARE TRUST LEAD PRESCRIBING SUPPORT PHARMACIST/DIRECTOR v SANOFI-SYNTHELABO and BRISTOL-MYERS SQUIBB

Plavix journal advertisement

The lead prescribing support pharmacist at a primary care trust alleged that a journal advertisement for Plavix (clopidogrel) issued jointly by Bristol-Myers Squibb and Sanofi-Synthelabo was misleading. The advertisement stated: 'Imagine you've had a heart attack, stroke or have PAD [peripheral arterial disease], Imagine you've been prescribed aspirin, imagine improving on that. Plavix delivers significant protection above and beyond aspirin'.

The complainant stated that the advertisement was based entirely upon the outcomes of the CAPRIE study in which patients with a history of heart attack, stroke or PAD were randomised to aspirin or Plavix and followed up for a composite primary outcome of ischaemic stroke, heart attack or vascular death. The study showed a significant reduction in risk in the Plavix group. However, in a pre-defined subgroup analysis statistically significant benefit was only demonstrated in the PAD subgroup. In the stroke subgroup a non-significant trend towards benefit was shown and in the heart attack subgroup the trend was towards harm but again this was not significant.

The complainant stated that the advertisement could be interpreted as Plavix being significantly better than aspirin in preventing ischaemic stroke, heart attack or vascular death in any patient who had had either a heart attack or a stroke. The CAPRIE study did not show this to be the case.

When writing to the companies the Authority noted that the complaint appeared to be closely similar to Cases AUTH/889/6/99 and AUTH/890/6/99. This raised the possibility of a breach of undertaking which was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice given by the Code of Practice Appeal Board.

The Panel noted that CAPRIE was designed to assess the relative efficacy of Plavix and aspirin in reducing the risk of a composite outcome cluster of ischaemic stroke, heart attack or vascular death. The population studied comprised subgroups of patients with atherosclerotic vascular disease namely recent ischaemic stroke, recent heart attack or symptomatic PAD. Most of the patients who had had a recent heart attack received aspirin for the first few days immediately following their heart attack. The study was powered to detect a realistic treatment effect in the whole study cohort but not in each of the three clinical subgroups. The primary endpoint showed a statistically significant relative risk reduction in favour of Plavix. The study authors stated that the long-term administration of Plavix to patients with atherosclerotic vascular disease was more effective than aspirin in reducing the combined risk of ischaemic stroke, heart attack or vascular death. Analyses of the heart attack, stroke, and PAD subgroups showed a relative risk reduction of –3.7%, 7.3% and 23.8% respectively. The study authors stated that a test for heterogeneity suggested that the observed differences in these relative treatment effects were greater than might be due to chance. The 'Pharmacodynamic properties' section of the Plavix summary of product characteristics (SPC) stated that in patients who were enrolled in the trial on the sole basis of a recent heart attack, Plavix was numerically inferior, but not statistically different from aspirin. It was further stated that since the CAPRIE trial was not powered to evaluate efficacy in individual subgroups, it was not clear whether the differences in relative risk reduction across qualifying conditions were real, or a result of chance.

The Panel thus did not consider that the results of the CAPRIE study demonstrated a clear outcomes benefit for patients when analysed by qualifying condition ie patients who had had a recent stroke or heart attack or PAD if treated with Plavix instead of aspirin; the study was not powered to evaluate efficacy in individual subgroups. The Panel considered that the advertisement was misleading in that regard and that the implied claim for benefit compared with aspirin in subgroups of patients could not be substantiated. Breaches of the Code were thus ruled.

Upon appeal by Bristol-Myers Squibb and Sanofi-Synthelabo the Appeal Board noted that Plavix was licensed for the prevention of atherothrombotic events in patients who had had a recent heart attack, ischaemic stroke or who had established PAD. These were all clinical manifestations of atherosclerotic vascular disease. The CAPRIE study assessed the relative long-term efficacy of Plavix and aspirin in patients with atherosclerotic vascular disease. Plavix was shown to be more effective than aspirin in reducing the combined risk of ischaemic stroke, myocardial infarction or vascular death. Patients were enrolled into the study if they had had a recent ischaemic stroke, a recent heart attack or had symptomatic PAD. The study was powered to detect an effect in the whole patient cohort but not in each of the three clinical subgroups. The Appeal Board noted that the CAPRIE study was an important study and although Plavix prevented atherothrombotic events in patients who had had a heart attack, stroke or who had PAD, as per the licensed indications, it had not shown it to be more efficacious than aspirin in each of these three separate patient subgroups, only in the patient population as a whole.

The Appeal Board noted that the advertisement stated 'Imagine you've had a heart attack, stroke or have PAD, imagine you've been prescribed aspirin, imagine improving on that. Plavix delivers significant protection above and beyond aspirin'.

The Appeal Board accepted that patients with one manifestation of atherosclerotic vascular disease would often develop another and that there was thus an overlap between the clinical subgroups. Nonetheless, the Appeal Board considered that the advertisement implied that any patient who presented with a heart attack or with a stroke or with PAD would have a better outcome on Plavix than on aspirin. This had not been proven. The Appeal Board considered that the advertisement was misleading in this regard and upheld the Panel's ruling of breaches of the Code.

With regard to the possible breach of undertaking the Panel noted that in Cases AUTH/889/6/99 and AUTH/890/6/99 breaches of the Code had been ruled because of claims, based on the results of the CAPRIE study, that compared to aspirin, Plavix was significantly more effective at reducing heart attack, reducing stroke and reducing vascular death, which was not so. The Panel considered that the advertisement now at issue was sufficiently different for it not to be in breach of the undertaking given in Cases AUTH/889/6/99 and AUTH/890/6/99. No breaches of the Code were ruled.

The lead prescribing support pharmacist at a primary care trust complained about a journal advertisement (ref PLA03/257) for Plavix (clopidogrel) issued jointly by Bristol-Myers Squibb Pharmaceuticals Limited and Sanofi-Synthelabo Limited.

When writing to the companies the Authority noted that the complaint appeared to be closely similar to a previous complaint (Cases AUTH/889/6/99 and AUTH/890/6/99). This raised the possibility of a breach of undertaking which was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice given by the Code of Practice Appeal Board.

COMPLAINT

The complainant noted that the body of the advertisement stated:

'Imagine you've had a heart attack, stroke or have PAD [peripheral arterial disease], Imagine you've been prescribed aspirin, imagine improving on that. Plavix delivers significant protection above and beyond aspirin'.

The complainant had contacted Sanofi-Synthelabo to confirm that the advertisement was based entirely upon the outcomes of the CAPRIE study in which patients with a history of heart attack, stroke or PAD were recruited and randomised to aspirin or Plavix and followed up for a composite primary outcome of ischaemic stroke, heart attack or vascular death. In this instance there was a significant reduction in risk in the Plavix group. However, a pre-defined subgroup analysis looked at the recruited disease types separately. In these subgroups, statistically significant benefit was only demonstrated in the PAD group. In the stroke group a trend towards benefit was shown but this was not significant and in the heart attack group the trend was towards harm but again this was not significant.

The complainant alleged that the advertisement was misleading in that it could be interpreted as Plavix being significantly better than aspirin in preventing ischaemic stroke, heart attack or vascular death in any patient who had had either a heart attack or a stroke. The study upon which this advertisement was based did not show this to be the case in the subgroup analysis.

When writing to the companies the Authority asked them to respond in relation to Clauses 2, 7.2, 7.4, 9.1 and 22.

RESPONSE

Bristol-Myers Squibb and Sanofi-Synthelabo submitted a joint response. The companies stated that Cases AUTH/889/6/99 and AUTH/890/6/99 involved the outcomes from CAPRIE (heart attack, ischaemic stroke or peripheral arterial disease), whereas the complaint now at issue (Cases AUTH/1588/5/04 and AUTH/1589/5/04) involved patient populations included in CAPRIE. The Plavix summary of product characteristics (SPC) stated that Plavix was indicated for the prevention of atherothrombotic events in patients suffering from a heart attack (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral vascular disease. These were the populations referred to in the text in the body of the advertisement. The prescribing information at the bottom of the advertisement read 'Indication: Reduction of atherothrombotic events in patients with a history of symptomatic atherosclerotic disease defined by ischaemic stroke, myocardial infarction (MI) [heart attack] or established peripheral arterial disease …'. Patients presented to their doctor with either stroke, heart attack or PAD as a manifestation of atherothrombotic disease and if prescribed Plavix, rather than aspirin, had a significantly reduced risk of either further stroke, heart attack and PAD. The licence for use of Plavix was not confined to patients presenting with all three conditions and it was therefore difficult to understand how this advertisement could be construed as misleading, given the current understanding of risk across all clinical presentations.

The companies submitted that the text was consistent with the SPC and prescribing information and as such the advertisement was not misleading, therefore no breach of Clauses 7.2 and 7.4 could be ruled.

The companies stated that as a result of Cases AUTH/889/6/99 and AUTH/890/6/99 all materials were removed and the copy had subsequently been altered to be consistent with the ruling made in those cases and consistent with the SPC. The companies thus denied breaches of Clauses 2, 9.1 and 22.

PANEL RULING

The Panel considered that the advertisement implied that any patient who had had a heart attack or a stroke or who had PAD, would have a better outcome if they were treated with Plavix instead of aspirin. This claim had been made on the basis of the results of the CAPRIE study.

The Panel noted that CAPRIE was a randomised blinded trial designed to assess the relative efficacy of Plavix (75mg once daily) and aspirin (325mg once daily) in reducing the risk of a composite outcome cluster of ischaemic stroke, heart attack or vascular death. The population studied comprised subgroups of patients with atherosclerotic vascular disease namely recent ischaemic stroke, recent heart attack or symptomatic peripheral arterial disease. Most of the patients who had had a recent heart attack received aspirin for the first few days immediately following their heart attack. The study was powered to detect a realistic treatment effect in the whole study cohort but not in each of the three clinical subgroups. The primary endpoint showed a statistically significant relative risk reduction in favour of Plavix. The study authors stated that the long-term administration of Plavix to patients with atherosclerotic vascular disease was more effective than aspirin in reducing the combined risk of ischaemic stroke, heart attack or vascular death. Analyses of the heart attack, stroke, and PAD subgroups showed a relative risk reduction of –3.7%, 7.3% and 23.8% respectively. The study authors stated that a test for heterogeneity suggested that the observed differences in these relative treatment effects were greater than might be due to chance. The 'Pharmacodynamic properties' section of the Plavix SPC stated that in patients who were enrolled in the trial on the sole basis of a recent heart attack, Plavix was numerically inferior, but not statistically different from aspirin. It was further stated that since the CAPRIE trial was not powered to evaluate efficacy in individual subgroups, it was not clear whether the differences in relative risk reduction across qualifying conditions were real, or a result of chance.

The Panel thus did not consider that the CAPRIE study demonstrated a clear outcomes benefit for patients when analysed by qualifying condition ie patients who had had a recent stroke or heart attack or PAD if treated with Plavix instead of aspirin; the study was not powered to evaluate efficacy in individual subgroups. The Panel considered that the advertisement was misleading in that regard and that the implied claim for benefit compared with aspirin in subgroups of patients could not be substantiated. Breaches of Clauses 7.2 and 7.4 were thus ruled. This ruling was appealed by Bristol-Myers Squibb and Sanofi-Synthelabo.

The Panel noted that in Cases AUTH/889/6/99 and AUTH/890/6/99 breaches of the Code had been ruled because a detail aid and an advertisement featured claims, based on the results of the CAPRIE study, that compared to aspirin, Plavix was significantly more effective at reducing heart attack, reducing stroke and reducing vascular death, which was not so. The Panel considered that in that regard the advertisement now at issue was sufficiently different for it not to be in breach of the undertaking given in Cases AUTH/889/6/99 and AUTH/890/6/99. No breach of Clauses 2, 9.1 and 22 was ruled.

APPEAL BY BRISTOL-MYERS SQUIBB AND SANOFI-SYNTHELABO

The indications for Plavix in the SPC were '…the prevention of atherothrombotic events in patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease'.

The advertisement stated 'Imagine you've had a heart attack, stroke or PAD [peripheral arterial disease] …'.

The companies noted that the patient groups in the advertisement were consistent with the licensed indication and the order in which they were mentioned was the same as in the SPC. The companies further noted that the indications (heart attack, stroke or PAD) were listed in one line rather than being split into three lines (ie 'imagine you've had a heart attack, imagine you've had a stroke, imagine you have peripheral arterial disease'). This accurately represented those groups of patients that were recruited into the CAPRIE study, and reflected in the SPC, and also combined them in a single cohort by listing them on one line. By the format of the wording adopted the advertisement did not invite an analysis of subgroups. The claim was, therefore, consistent with the SPC and as the wording reflected the SPC in the format laid out in the SPC, it was not misleading.

The companies stated that CAPRIE was designed to study a cohort of atherothrombotic patients and evaluate efficacy by assessing differences in a composite endpoint (atherothrombotic events: myocardial infarction, ischaemic stroke and vascular death) between Plavix and aspirin. The SPC (Section 5.1) stated that 'since the CAPRIE trial was not powered to evaluate efficacy of individual subgroups, it is not clear whether the differences in relative risk reduction across qualifying conditions are real, or a result of chance'.

The companies submitted that conclusions from the subgroup analyses were limited by the smaller numbers analysed. The most robust and valid interpretation of the CAPRIE study therefore was to consider the whole cohort recruited and the primary endpoint (the outcome cluster of reduction of atherothrombotic events) and, in doing so, it was shown that Plavix was significantly superior to aspirin in reducing atherothrombotic events (myocardial infarction, ischaemic stroke and vascular death) in patients with vascular disease (myocardial infarction, ischaemic stroke and peripheral arterial disease).

The companies submitted that the advertisement was thus consistent with the conclusion drawn from CAPRIE and, importantly, consistent with the particulars listed in the SPC.

The companies disagreed that the wording in the advertisement was not substantiable as they had highlighted that the advertisement was based on CAPRIE and the conclusion was drawn from the study. Furthermore, as demonstrated above, the wording of the advertisement reflected the licensed indications stated in the SPC and, as stated in Clause 7.5 of the Code, substantiation did not need to be provided 'in relation to the validity of indications approved in the marketing authorization'.

The companies submitted that the complainant had misinterpreted the advertisement, especially in the

light of evidence that emphasised the risk of future vascular events in multiple vascular beds in patients such as those studied in CAPRIE and the nature of the global vascular disease represented by such a study.

COMMENTS FROM THE COMPLAINANT

The complainant agreed that the advertisement was in keeping with the SPC and accurately reflected the primary study group of CAPRIE. However he disagreed with the submission that the advertisement did not invite a subgroup analysis just because it used the same wording and same ordering as both the SPC and the CAPRIE study.

The complainant noted that the companies had based the advertisement on the CAPRIE study and the SPC referenced this study. The study had fully detailed a subgroup analysis under the method heading. The original trial might not have been powered to detect differences at the subgroup level, but in this case why define these analyses in the design of the trial and allow them to dominate the content of the paper?

The complainant submitted that medical practitioners who chose to look up the reference in the SPC would find it plain to read that the data were presented repeatedly through the paper in subgroup categories. Therefore, to suggest that an advertisement based on CAPRIE did not invite an analysis of subgroups seemed to be a strange argument, perhaps readers of the advertisement were not expected to look at the paper at all!

The complainant noted that on the basis of the whole study population Plavix was statistically better than aspirin, but stated that during a patient consultation a medical practitioner would assess a patient with a single diagnosis from the list of three included in the advertisement. By implication the advertisement stated that Plavix was better than aspirin in these single disease areas even though, by the companies' own admission, they could not substantiate these claims as the CAPRIE study was not powered to detect differences in the subgroups detailed in the paper.

The complainant alleged that purely listing the disease areas together on a single line, in accordance with the SPC, would not stop readers seeing the three individual diseases. There was no individual patient that was representative of the primary trial cohort and therefore the advertisement invited a subgroup analysis.

The complainant noted that the companies had disagreed that the wording of the advertisement was not substantiable. Again the complainant noted that by their own admission the companies could not demonstrate significantly better outcomes from aspirin for individuals with single disease diagnoses.

The complainant considered that the companies' statement that 'the complainant had misinterpreted the advertisement' was an admission that the advertisement was misleading. As he had managed to read something into the advertisement that was not intended to be stated without any extrapolation of information on his part proved that the advertisement was misleading.

The complainant stated that the companies were entitled to advertise and promote Plavix within the bounds of its SPC. The original trial design for the CAPRIE was to recruit patients with a history of ischaemic events. Since the study looked at subgroups and a test of heterogenicity was performed that suggested that the benefit of Plavix might not be identical across the three groups, claims could not and should not be made for a list of conditions. This inferred equivalent benefit for each of the diseases stated in the list, and the complainant restated that this could not be substantiated.

The complainant stood by his original complaint that the advertisement was misleading.

APPEAL BOARD RULING

The Appeal Board noted that Plavix was licensed for the prevention of atherothrombotic events in patients who had had a recent heart attack, ischaemic stroke or who had established PAD. These were all clinical manifestations of atherosclerotic vascular disease. The CAPRIE study assessed the relative long-term efficacy of Plavix and aspirin in patients with atherosclerotic vascular disease. Plavix was shown to be more effective than aspirin in reducing the combined risk of ischaemic stroke, myocardial infarction or vascular death. Patients were enrolled into the study if they had had a recent ischaemic stroke, a recent heart attack or had symptomatic PAD. The study was powered to detect an effect in the whole patient cohort but not in each of the three clinical subgroups. The Appeal Board noted that the CAPRIE study was an important study and although Plavix prevented atherothrombotic events in patients who had had a heart attack, stroke or who had PAD, as per the licensed indications, it had not shown it to be more efficacious than aspirin in each of these three separate patient subgroups, only in the patient population as a whole.

The Appeal Board noted that the advertisement stated 'Imagine you've had a heart attack, stroke or have PAD, imagine you've been prescribed aspirin, imagine improving on that. Plavix delivers significant protection above and beyond aspirin'. The Appeal Board accepted that patients with one manifestation of atherosclerotic vascular disease would often develop another and that there was thus an overlap between the clinical subgroups. Nonetheless, the Appeal Board considered that the advertisement implied that any patient who presented with a heart attack or with a stroke or with PAD would have a better outcome on Plavix than on aspirin. This had not been proven. The Appeal Board considered that the advertisement was misleading in this regard and upheld the Panel's ruling of breaches of Clauses 7.2 and 7.4 of the Code. The appeal was unsuccessful.

Complaint received **5 May 2004**

Case completed **7 October 2004**

CASE AUTH/1590/5/04

PRIMARY CARE TRUST DIRECTOR OF CLINICAL GOVERNANCE v GLAXOSMITHKLINE

Rosiglitazone (Avandia and Avandamet) journal advertisement

The director of clinical governance at a primary care trust complained about a journal advertisement issued by GlaxoSmithKline which discussed rosiglitazone and its availability as Avandia and, with metformin, as Avandamet. Both products were indicated for glycaemic control in certain groups of type 2 diabetics.

The complainant believed that a statement that rosiglitazone helped to control blood pressure compared with sulphonylureas, which had no such effect, was misleading and was not substantiated by clinical evidence.

The Panel noted that whilst the advertisement did not contain a discrete statement that 'rosiglitazone helped to control blood pressure compared with sulphonylureas', as implied by the complainant, it nonetheless directly compared the two with regard to blood pressure control.

The Panel noted GlaxoSmithKline had referred to Case AUTH/1580/4/04 wherein the same advertisement was the subject of a recent adjudication by the Code of Practice Panel; GlaxoSmithKline had not been informed of the outcome of that case before it had submitted its response to this case. The complainant in Case AUTH/1580/4/04 had been concerned about the claim that using rosiglitazone could help to lower blood pressure and queried whether this supposedly additional benefit could be advertised in this manner. The Panel had noted that the advertisement was headed 'Confront the new challenges for Type 2 diabetes' and referred to rosiglitazone available as Avandia and, in combination with metformin, as Avandamet. Avandia could be used as monotherapy particularly in overweight patients inadequately controlled by diet and exercise and for whom metformin was inappropriate. It could also be used in combination treatment in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea. Avandamet was indicated for the treatment of type 2 diabetics, particularly overweight patients, who were unable to achieve sufficient glycaemic control at their maximally tolerated dose of metformin alone.

The Panel had noted in Case AUTH/1580/4/04 that the introductory paragraph of the advertisement stated that managing type 2 diabetes was no longer just about glycaemic control and that this was why the General Medical Services (GMS) contract focussed 'on both lasting glycaemic control and reductions in blood pressure'. The remainder of the paragraph discussed tight glycaemic control and its association with fewer microvascular complications and tight blood pressure control and its association with fewer major cardiovascular events.

The following paragraph had explained that rosiglitazone could help meet both blood glucose and blood pressure GMS targets by targeting insulin resistance, a root cause of type 2 diabetes. A subsequent paragraph began 'By targeting insulin resistance, rosiglitazone also helps to achieve blood pressure targets …' and discussed studies which had consistently shown that rosiglitazone helped to significantly lower blood pressure. The effect of rosiglitazone on blood pressure was compared to that of sulphonylureas and it was further noted that the 'UKPDS [UK Prospective Diabetes Study] found that sulphonylureas had no significant effect on cardiovascular outcomes after a mean treatment period of 10 years'. The final paragraph referred to Avandia and Avandamet. The claims 'You really want to hit targets year after year' and 'Using the right oral antidiabetic agent can also help lower blood pressure' appeared in highlighted circles. The Panel considered that there was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition.

The Panel had noted that there was evidence showing a beneficial effect of Avandia on blood pressure in type 2 diabetics. Whilst it was not necessarily unacceptable to refer to such a benefit in promotional material such references should comply with the Code and could only be made within the context of treating patients for the product's licensed indications. The Panel considered that the balance of the advertisement was such that the reduction of blood pressure as a benefit of using Avandia or Avandamet had been given undue emphasis; such an effect had not been placed sufficiently within the context of the licensed indications for the products. The advertisement implied that Avandia and Avandamet were indicated for blood pressure reduction and that was not so; the advertisement was misleading and inconsistent with the marketing authorizations in this regard. Breaches of the Code had been ruled.

Turning to the present case, Case AUTH/1590/4/04, the Panel considered that whilst the allegation was different to that considered previously, its comments in Case AUTH/1580/4/04 were nonetheless relevant.

The Panel considered that the balance of the advertisement was such that undue emphasis had been given to the reduction of blood pressure as a benefit of using Avandia and Avandamet; it implied that Avandia and Avandamet were so licensed which was not so. Whilst it was not necessarily unacceptable to compare the blood pressure lowering effect of sulphonylureas and rosiglitazone any such comparisons could only be made within context of treating patients for the products' licensed indications. The Panel considered that given the balance of the advertisement the comparison at issue compounded the overall misleading impression that Avandia and Avandamet were licensed for reduction of blood pressure. A breach of the Code was ruled.

The director of clinical governance at a primary care trust complained about a journal advertisement (ref AVM/FPA/04/11822/1) issued by GlaxoSmithKline UK Ltd which appeared in Pulse 12 April. The advertisement discussed rosiglitazone and its availability as Avandia and, with metformin, as Avandamet. Both products were indicated for glycaemic control in certain groups of type 2 diabetics.

COMPLAINT

The complainant believed that a statement that rosiglitazone helped to control blood pressure compared with sulphonylureas, which had no such effect, was misleading and was not substantiated by clinical evidence.

When writing to GlaxoSmithKline, the Authority invited it to respond in relation to Clause 7.2 of the Code of Practice.

RESPONSE

GlaxoSmithKline explained that in a recent review of the glitazones, the Medicines and Healthcare products Regulatory Agency (MHRA) had acknowledged that promotion of the effects of glitazones on blood pressure was consistent with the marketing authorization for these agents; and explicitly that the evidence base was sufficient to justify such promotion. Specifically it stated that 'The evidence shows that glitazones may have a secondary effect on other parameters such as modifying blood lipids and blood pressure, in diabetic patients, though it does not conclude whether these effects are due to a direct or an indirect (through its insulin-sensitising) action'. The advertisement in question did not fall outside the MHRA guidelines, a copy of which was provided.

The importance of vigorously addressing raised blood pressure in type 2 diabetics was indisputable. The United Kingdom Prospective Diabetes Study (UKPDS) – the only major prospective outcome study in this condition conducted to date – demonstrated that tight blood pressure control was the single most important factor in reducing the incidence of macrovascular complications, including myocardial infarction, stroke and sudden death. Thus there was a 34% reduction in adverse cardiovascular outcomes in the tight blood pressure control group compared with the 'standard' control group. However, the study also demonstrated the difficulty of achieving optimum control: nearly 45% of patients in the tight control group failed to maintain their target blood pressure; and 60% of hypertensive patients needed two or more antihypertensive agents, and 29% three or more agents, to maintain adequate control. In this context, the ancillary antihypertensive effects of an antidiabetic agent such as rosiglitazone contained in both Avandia and Avandamet were highly relevant.

The Oxford Handbook of Endocrinology and Diabetes (2002 edition) stated that hypertension in type 2 diabetes was associated with both insulin resistance and hyperinsulinaemia. Hyperinsulinaemia might directly cause hypertension by increasing sympathetic nervous system activity, stimulating proximal tubule sodium resorption and stimulating vascular smooth muscle cell proliferation. Sulphonylureas, which stimulated release of insulin from pancreatic beta cells, would therefore not be expected to positively affect blood pressure, and this was borne out in the conclusions of a number of articles eg Inzucchi (2002) and Fonseca (2003). In contrast, agents that reduced insulin resistance such as rosiglitazone might be expected to have positive effects on blood pressure (Viberti *et al* 2003) and this was borne out by clinical data.

The UKPDS demonstrated that sulphonylureas had no significant effect on blood pressure. In UKPDS 33 'systolic and diastolic blood pressure were significantly higher throughout the study in patients assigned chlorpropamide than in those assigned any of the other therapies'.

Evidence that sulphonylureas as a class had no effect on blood pressure compared to rosiglitazone was backed up by data from a comparative study of glibenclamide with rosiglitazone (St John Sutton *et al* 2002) wherein rosiglitazone was associated with significant reductions in blood pressure compared to glibenclamide (drops of 3.7/2.8mmHg v glibenclamide at a mean dose of 10.5mg over 1 year). A double-blind, placebo controlled trial designed to measure changes in blood pressure with the addition of rosiglitazone therapy demonstrated blood pressure reductions of 12/6mmHg (Honisett *et al* 2003). These two studies, together with a number of others, provided a growing body of evidence relating to the blood pressure lowering effects of targeting insulin resistance. GlaxoSmithKline provided details of the reductions seen with rosiglitazone in 11 studies.

GlaxoSmithKline submitted that as this case was similar to Case AUTH/1580/4/04 it seemed sensible for any ruling to be considered in the light of the ruling in the earlier case. In summary GlaxoSmithKline did not agree that Clause 7.2 of the Code had been breached. The benefits of blood pressure lowering were clear from the UKPDS study and agents such as rosiglitazone that had ancillary blood pressure lowering effects in addition to blood glucose lowering offered important clinical advantages. The UKPDS study had demonstrated that sulphonylureas had no significant blood pressure lowering effects. St John Sutton *et al* confirmed that rosiglitazone offered advantages over sulphonylurea therapy with respect to blood pressure control, and a number of other studies now added to the body of evidence on the blood pressure lowering effects of rosiglitazone.

GlaxoSmithKline stated that the advertisement to which the complainant referred had been withdrawn in the week commencing 10 May as part of a planned campaign update.

PANEL RULING

The Panel noted that whilst the advertisement did not contain a discrete statement that 'rosiglitazone helped to control blood pressure compared with sulphonylureas', as implied by the complainant, it nonetheless directly compared the two with regard to blood pressure control. The Panel also noted that

GlaxoSmithKline had not been notified of the outcome of the previous case, Case AUTH/1580/4/04, when it submitted its response to the present complaint.

Case AUTH/1580/4/04

The Panel noted GlaxoSmithKline had referred to Case AUTH/1580/4/04 wherein the same advertisement was the subject of a recent adjudication by the Code of Practice Panel; the complainant had been concerned about the claim that using rosiglitazone could help to lower blood pressure and queried whether this supposedly additional benefit from rosiglitazone could be advertised in this manner. The Panel had noted that the advertisement was headed 'Confront the new challenges for Type 2 diabetes' and referred to rosiglitazone available as Avandia and, in combination with metformin, as Avandamet. Avandia was indicated as oral monotherapy treatment of type 2 diabetics particularly in overweight patients inadequately controlled by diet and exercise and for whom metformin was inappropriate because of contraindications or intolerance. Avandia was also indicated in oral combination treatment in patients 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 who showed intolerance to metformin or for whom metformin was contraindicated. Avandamet was indicated for the treatment of type 2 diabetics, particularly overweight patients, who were unable to achieve sufficient glycaemic control at their maximally tolerated dose of metformin alone.

The Panel had noted that the introductory paragraph of the advertisement stated that managing type 2 diabetes was no longer just about glycaemic control and that this was why the GMS contract focussed 'on both *lasting* glycaemic control and reductions in blood pressure'. The remainder of the paragraph discussed tight glycaemic control and its association with fewer microvascular complications and tight blood pressure control and its association with fewer major cardiovascular events.

The following paragraph explained that rosiglitazone could help meet both blood glucose and blood pressure GMS targets by targeting insulin resistance, a root cause of type 2 diabetes. Reference was made to hitting 'targets year after year' within the context of rosiglitazone's 'proven lasting effectiveness'. A subsequent paragraph began 'By targeting insulin resistance, rosiglitazone also helps to achieve blood pressure targets …' and discussed studies which had consistently shown that rosiglitazone helped to significantly lower blood pressure. The effect of rosiglitazone on blood pressure was compared to that of sulphonylureas and it was further noted that the 'UKPDS found that sulphonylureas had no significant effect on cardiovascular outcomes after a mean treatment period of 10 years'. The final paragraph referred to Avandia and Avandamet. The claims 'You really want to hit targets year after year' and 'Using the right oral antidiabetic agent can also help lower blood pressure' appeared in highlighted circles.

The Panel had considered there was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition.

The Panel had noted that there was evidence showing a beneficial effect of Avandia on blood pressure in type 2 diabetics. Whilst it was not necessarily unacceptable to refer to such a benefit in promotional material such references should comply with the Code and could only be made within the context of treating patients for the product's licensed indications. The Panel considered that the balance of the advertisement was such that the reduction of blood pressure as a benefit of using Avandia or Avandamet had been given undue emphasis. The advertisement did not place reduction in blood pressure sufficiently within the context of the licensed indications for the products. The advertisement gave the impression that Avandia and Avandamet were indicated for blood pressure reduction and that was not so; the advertisement was misleading and inconsistent with the marketing authorizations in this regard. Breaches of Clauses 3.2 and 7.2 had been ruled.

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Case AUTH/1590/4/04

Turning to the present case, Case AUTH/1590/4/04, the Panel considered that whilst the allegation was different to that considered previously its comments in Case AUTH/1580/4/04 were nonetheless relevant. The Panel noted the licensed indications of Avandia and Avandamet as set out above. The Panel noted that sulphonylureas were indicated for the treatment of type 2 diabetes (ref BNF March 2004).

The Panel noted GlaxoSmithKline's submission about the importance of addressing raised blood pressure in type 2 diabetics and that the UKPDS demonstrated that sulphonylureas had no significant blood pressure lowering effects.

The Panel considered that the balance of the advertisement was such that undue emphasis had been given to the reduction of blood pressure as a benefit of using Avandia and Avandamet; it gave the impression that Avandia and Avandamet were so licensed. That was not so. Whilst it was not necessarily unacceptable to compare the blood pressure lowering effect of sulphonylureas and rosiglitazone any such comparisons could only be made within the context of treating patients for the products' licensed indications. The Panel considered that given the balance of the advertisement the comparison at issue compounded the overall impression that Avandia and Avandamet were licensed for reduction of blood pressure. The comparison was misleading in this regard. A breach of Clause 7.2 was ruled.

Complaint received **13 May 2004**

Case completed **5 July 2004**

CASE AUTH/1591/5/04

JANSSEN-CILAG v NAPP

Promotion of Transtec

Janssen-Cilag complained about a detail aid and a leavepiece for Transtec (buprenorphine transdermal patch) issued by Napp. Transtec was indicated for moderate to severe cancer pain and severe pain which did not respond to non-opioid analgesics. Janssen-Cilag supplied Durogesic (fentanyl transdermal patch). Durogesic was indicated for the management of chronic intractable pain due to cancer or otherwise. Section 4.2 of the Durogesic summary of product characteristics (SPC) stated that in strong opioid naïve patients, the lowest dose 25µg/hr should be used as the initial dose.

Janssen-Cilag noted the claim 'Transtec matrix patches can be used sooner than [Durogesic]' was followed by an approximation to the morphine equivalence of each medicine and another claim 'Transtec's low starting dose means that it may be appropriate to use before fentanyl in strong opioid naïve patients'. Janssen-Cilag alleged that to imply that there were some patients for whom the lowest dose of Transtec (35mg/hr) was suitable but the lowest dose of Durogesic (25µg/hr) was not suitable, was misleading, incapable of substantiation and disparaged Durogesic.

The Panel noted that according to their respective SPCs the lowest strength Transtec patch (35µg/hr) was equivalent to 30-60mg oral morphine per day and the lowest strength Durogesic patch (25µg/hr) was equivalent to oral doses of morphine of less than 135 mg/day. Under the heading dose titration the Durogesic SPC stated that Durogesic 25µg/hr was approximately equivalent to 90mg/day of oral morphine. The Panel acknowledged that there was a difference between the products in that the lowest strength Transtec patch was less potent than the lowest strength Durogesic patch. The Transtec SPC indicated that the product could be used in patients who had previously not received any analgesics whereas the Durogesic SPC stated that the initial dose should be based, *inter alia*, on the patient's opioid history. The Panel noted, however, that both the detail aid and the leavepiece referred, on their front covers, to Transtec as 'Your next step after a weak opioid in severe, chronic pain' and it was in this context that the claims at issue were considered.

Both the detail aid and the leavepiece stated that 'Transtec matrix patches can be used sooner than [Durogesic] patches'. There then followed a description of the oral morphine equivalent of the lowest strength of both products. This was followed by the claim 'Transtec's low starting dose means it may be appropriate to use before [Durogesic] in strong opioid naïve patients'. The Panel noted Napp's submission with regard to the difference between the equivalent daily oral morphine dose for the two products and clinical practice. Nonetheless, Durogesic 25µg/hr was licensed for use in patients who had not previously received a strong opioid. This was not made sufficiently clear in the materials. The Panel considered that use of the word 'may' in the claim that Transtec '*may* (emphasis added) be appropriate to use before [Durogesic]' did not negate the impression that Transtec was appropriate to use before Durogesic. Given the licensed indications for both products with regard to patients who needed more than a weak opioid, the Panel considered that, in the context in which they appeared, the claims 'Transtec matrix patches can be used sooner than fentanyl reservoir patches' and 'Transtec's low starting dose means that it may be appropriate to use before fentanyl in strong opioid naïve patients' were misleading and could not be substantiated. Breaches of the Code were ruled. The Panel further considered that the claims disparaged Durogesic. A breach of the Code was ruled.

Janssen-Cilag Ltd complained about the promotion of Transtec (buprenorphine transdermal patch) by Napp Pharmaceuticals Limited. The items at issue were a leavepiece (ref UK/TR-03052) and a detail aid (ref UK/TR-03048) which had been used with both primary and secondary care health professionals between 1 January and 30 April 2004. Transtec was indicated for moderate to severe cancer pain and severe pain which did not respond to non-opioid analgesics. Janssen-Cilag supplied Durogesic (fentanyl transdermal patch). Durogesic was indicated for the management of chronic intractable pain due to cancer or otherwise. Contact between the companies had failed to resolve the matter.

COMPLAINT

Janssen-Cilag noted that Napp had made several claims on the 'theme' that Transtec could be used before Durogesic. The claims started with 'Transtec matrix patches can be used sooner than fentanyl reservoir patches'. This was then followed by an approximation to the morphine equivalence of each medicine, and another claim stating 'Transtec's low starting dose means that it may be appropriate to use before fentanyl in strong opioid naïve patients'. Janssen-Cilag alleged that these claims were misleading, incapable of substantiation and disparaged Durogesic in breach of Clauses 7.2, 7.4 and 8.1 of the Code.

The summary of product characteristics (SPC) clearly stated that Durogesic was indicated in the management of chronic intractable cancer and non-cancer pain. Section 4.2 of the SPC stated that in strong opioid naïve patients, the lowest Durogesic dose 25µg/hr should be used as the initial dose.

The key question that needed to be addressed was: was there a patient population where Transtec could be used before/sooner than Durogesic?

Having compared the SPCs of both products Janssen-Cilag did not consider that such a patient population existed in either strong opioid naïve patients or opioid tolerant patients. Initiation of treatment with Durogesic 25µg/hr was wholly appropriate as long as the patient had chronic intractable cancer or non-cancer pain. The patient's current pain status was primarily determined clinically, taking into account their pre-existing

analgesic requirements. Durogesic treatment could be initiated in strong opioid naïve patients, and this by definition included patients who had not previously been exposed to morphine.

Transdermal buprenorphine was licensed for moderate to severe cancer pain and severe pain, which did not respond to non-opioid analgesics. Transdermal buprenorphine was contra-indicated for the treatment of acute pain.

Strong opioid naïve patients:

When a clinician had decided to initiate treatment with a strong opioid in a strong opioid naïve patient, there was no clinical instance where Transtec 35µg/hr could be used before/sooner than Durogesic 25µg/hr, which was a licensed dose for this patient group.

Opioid tolerant patients:

There were several guides to help clinicians who had decided to initiate treatment with a strong opioid in opioid tolerant patients. The Durogesic SPC stated that in patients requiring less than 135mg of oral morphine a day, Durogesic 25µg/hr was appropriate. The SPC further stated that subsequent dose adjustments should be made in 25µg/hr increments, although the supplementary analgesic requirements (oral morphine 90mg/day was approximately Durogesic 25µg/hr) and the pain status of the patient should be taken into account.

In patients who might have required, for example, either 10mg or 60mg of morphine previously per day, Durogesic 25µg/hr was an appropriate initial treatment dose. Although as previously stated the morphine conversion could serve as a guide, the key question to ask when a physician was deciding whether to commence therapy with Durogesic 25µg/hr in an opioid tolerant patient was: did the patient currently have chronic intractable cancer or non-cancer pain? If the answer was yes then Durogesic 25µg/hr was appropriate in patients whose previous oral morphine requirements were up to 135mg of morphine a day.

In conclusion, the overall decision to prescribe Durogesic 25µg/hr was based primarily on the clinical pain state of the patient. For opioid tolerant patients, the oral morphine conversion charts were there as a guide only. Accordingly, Napp's claims were misleading. Janssen-Cilag did not believe that Napp could substantiate its claim that there was a patient group where Transtec 35µg/hr could be used sooner/before Durogesic 25µg/hr in either strong opioid naïve patients or in opioid tolerant patients. Additionally, by implying that there were patients for whom Durogesic 25µg/hr was not suitable but Transtec 35µg/hr was, Napp disparaged Durogesic.

RESPONSE

Napp considered that the comparison made between Transtec and Durogesic complied with the Code. It was accurate, balanced, fair, objective, unambiguous, based on clear, up-to-date clinical recommendations to be found in a number of reputable publications and supported by leading authorities in pain management.

Napp noted that Janssen-Cilag's complaint was based exclusively on what its SPC stated. In the Durogesic SPC the overriding principle in initial dose selection was to take account of the patient's opioid history, their current general condition and medical status. Subject to that, the 25µg/hr patch was recommended as the initial dose for both strong opioid naïve patients and for opioid tolerant patients who had been taking up to 135mg of oral morphine a day. The section on dose titration, however, stated that the Durogesic 25µg/hr patch was equal to approximately 90mg of oral morphine per day.

The Transtec SPC advised that the lowest possible dose providing adequate pain relief should be given. For opioid naïve patients, this was the 35µg/hr patch. For those patients switching from an opioid analgesic, the guideline for conversion from oral morphine was as follows:

35µg/hr patch: 30-60mg of morphine.
52.5µg/hr patch: 90mg of morphine.
70µg/hr patch: 120mg of morphine.

A comparison of the data in the SPCs of the two products showed:

1 The lowest Transtec patch was equivalent to 30-60mg of oral morphine per day, whilst the lowest strength Durogesic patch was equivalent to 90mg of oral morphine per day. This compared to the recommended starting dose for MST Continus tablets of 60mg of morphine per day. A potency 50% greater than the starting dose for morphine was a clinically significant higher dose.

2 The 25 µg/hr Durogesic patch had the same morphine equivalence as the 52.5µg/hr Transtec patch ie the middle, not the lowest strength. This was further substantiated by Twycross *et al* (2003) Palliative Care Formulary which stated that 'buprenorphine 52.5 microgram/h is approximately equivalent to fentanyl TD 25 microgram/h'.

3 The highest strength Transtec patch had a morphine equivalence lower than the 135mg of morphine stated in the Durogesic SPC as the upper end of the range for which the 25µg/hr patch could be used.

Napp's first point was, therefore, that its claim, which was clearly referenced to the SPCs, did no more than draw a very obvious conclusion from a comparison of the morphine conversion rates for the two products.

This conclusion was further supported by what happened in clinical practice. Doctors were advised to carefully titrate patients on strong opioids to the optimum dosage level, and all the more so in opioid naïve, frail or vulnerable patients. 'Start low, go slow' was the principle. The aim was to minimise adverse effects, which was especially important when using controlled release products with prolonged retention times within the body. In other words, if too high a dose was given, resulting in side effects, the side effects would continue for many hours until the level of medicine in the body had reduced.

This was further supported in the introduction to the 1996 World Health Organisation (WHO) guidelines on cancer pain relief which stated 'the right drug in the

right dose at the right time intervals' and 'Low starting doses should be used in elderly people, who may have an increased response because of changes in the pharmacokinetics of opioids'. Perhaps the British National Formulary (BNF) provided the most commonly used guidance on current, recommended clinical practice. The preface to the BNF emphasised that it 'aims to provide prescribers, pharmacists and other healthcare professionals with sound up-to-date information about the use of medicines'. It was 'constructed from clinical literature and reflects, wherever possible, an evaluation of the evidence' and 'the Joint Formulary Committee receives expert clinical advice on all therapeutic areas in tune with correct best practice; this ensures that the BNF's recommendations are relevant to practice'. The BNF set out clear guidance on starting doses for strong opioids. In the section headed 'Prescribing in palliative care' the starting dose of twice daily modified release morphine preparations was described as '10-20mg every 12 hours if no other analgesic (or only paracetamol) has been taken previously, but to replace a weaker opioid analgesic (such as coproxamol) the starting dose is usually 20-30mg every 12 hours'. The BNF further stated under the heading 'Transdermal Route' that 'Careful conversion from oral morphine to transdermal fentanyl is necessary'. It then quoted a morphine equivalence of 90mg daily for the Durogesic 25µg/hr patch. This was consistent with the conversion level given in the titration section of the Durogesic SPC, and significantly higher than the starting dose for oral morphine.

Napp noted that the BNF guidance in the Transdermal Route section changed to the current wording in the September 2000 edition. Previously, in the March 2000 edition, it had stated that 'a 25 micrograms/hour patch is equivalent to a total dose of morphine up to 135mg/24 hours'. The reason for the change was unclear, but one reasonable inference was that in 2000, 5 years after launch, clinical practice recognised the need for a more precise conversion level between morphine and fentanyl than the previous statement (which reflected the SPC) that the lower strength fentanyl patch was equivalent to anything from 0.1mg to 135mg of morphine per day. This was not surprising given that this was a remarkably wide range of dosage of morphine which would be used to treat moderate pain at the lower end and severe pain at the higher end.

The current on-line version of Martindale, The Complete Drug Reference, also provided current clinical use for Transtec and Durogesic patches. For Transtec the 'Use of a patch providing 35 micrograms/hour of buprenorphine is approximately equivalent to the oral administration of 30 to 60 mg of morphine sulfate daily'. In contrast, for Durogesic, 'Use of a patch providing 25 micrograms of fentanyl per hour is approximately equivalent to oral administration of 90 mg of morphine sulfate daily'.

So, both the BNF and Martindale indicated that, in accordance with the SPCs, clinicians treated the lowest strength Transtec patch as being equivalent to a significantly lower dose of morphine than the lowest strength of the Durogesic patch. The Transtec lowest strength was considered to be approximately equivalent to the starting dose for modified release morphine, whilst the lowest strength Durogesic patch was considered to be 50% more potent and on a par with the middle strength Transtec patch.

The clinical significance of this could be seen from talking with experts in palliative care. Janssen-Cilag stated that there was no patient population in which Transtec patches could be used in preference to Durogesic. A senior lecturer in palliative medicine at a local cancer centre had provided the following comment based on her clinical experience. She cited, two important factors about Transtec in clinical practice:

1 'It is an opioid with clinical properties which are different from other opioids and we find useful in patients who are susceptible to opioid side effects'.

2 'It can be started at a relatively lower dose than some other opioids which is particularly useful in patients who cannot tolerate Step 2 analgesics but who have severe pain and problems with opioid side effects and need to be titrated gently. Such a drug is enormously helpful in clinical practice'.

A professor of anaesthesia, critical care and pain medicine at a local university stated that 'it is an advantage to patients and their clinicians to have available to them, in Transtec, a skin patch that can be used to provide a lower 'morphine equivalent' dose than the lowest dose Durogesic patch. Both are excellent preparations that can alleviate pain and suffering, but some patients can attain analgesia with minimal side-effects at lower opioid doses than others'.

In conclusion, there was nothing in the detail aid or leavepiece which denigrated Durogesic. The claim simply compared the SPCs of the two products and drew the obvious conclusion that the lowest strength Transtec patch was less potent than the lowest strength Durogesic patch. This conclusion was supported and further substantiated by clinical practice as evidenced by support from experts in cancer and non-cancer pain management, the BNF, Martindale and Twycross *et al*. This information was particularly relevant to a doctor seeking to carefully titrate a patient starting on a strong opioid patch, to assist him or her in achieving the optimum dose for the patient with the minimum side effects. The claim was accurate, fair and balanced. It reflected up-to-date clinical practice, as substantiated by clinicians, the BNF, Martindale and Twycross *et al*. Napp submitted that there was no breach of the Code.

PANEL RULING

The Panel noted that according to its SPC the lowest strength Transtec patch (35µg/hr) was equivalent to 30-60mg oral morphine per day. The lowest strength Durogesic patch (25µg/hr) was equivalent to oral doses of morphine of less than 135 mg/day according to part of section 4.1 of its SPC. Under the heading dose titration the SPC stated that Durogesic 25µg/hr was approximately equivalent to 90mg/day of oral morphine. The Panel acknowledged that there was a difference between the products in that the lowest

strength Transtec patch was less potent than the lowest strength Durogesic patch. The Transtec SPC indicated that the product could be used in patients who had previously not received any analgesics whereas the Durogesic SPC stated that the initial dose should be based, *inter alia*, on the patient's opioid history. The Panel noted, however, that both the detail aid and the leavepiece referred, on their front covers, to Transtec as 'Your next step after a weak opioid in severe, chronic pain' and it was in this context that the claims at issue were considered.

Both the detail aid and the leavepiece stated that 'Transtec matrix patches can be used sooner than [Durogesic] patches'. There then followed a description of the oral morphine equivalent of the lowest strength of both products. This was followed by the claim 'Transtec's low starting dose means it may be appropriate to use before [Durogesic] in strong opioid naïve patients'. The Panel noted Napp's submission with regard to the difference between the equivalent daily oral morphine dose for the two products and clinical practice. Nonetheless, Durogesic 25µg/hr was licensed for use in patients who had not previously received a strong opioid. This was not made sufficiently clear in the materials. The Panel noted that the claim stated that Transtec '**may** (emphasis added) be appropriate to use before [Durogesic]' but considered that use of the word 'may' did not negate the impression that Transtec **was** appropriate to use before Durogesic. Given the licensed indications for both products with regard to patients who needed more than a weak opioid, the Panel considered that, in the context in which they appeared, the claims 'Transtec matrix patches can be used sooner than fentanyl reservoir patches' and 'Transtec's low starting dose means that it may be appropriate to use before fentanyl in strong opioid naïve patients' were misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled. The Panel further considered that the claims disparaged Durogesic. A breach of Clause 8.1 was ruled.

Complaint received **14 May 2004**

Case completed **14 July 2004**

CASE AUTH/1592/5/04

GILEAD SCIENCES v GLAXOSMITHKLINE

Epivir and Ziagen leavepiece

Gilead Sciences complained about a leavepiece produced by GlaxoSmithKline which promoted Epivir (lamivudine) and Ziagen (abacavir) as an effective alternative nucleoside reverse transcriptase inhibitor (NRTI) backbone in treatment-naïve HIV patients. Gilead supplied two NRTIs, Viread (tenofovir) and Emtriva (emtricitabine).

Gilead alleged that the statement 'Oranges are not the only fruit. Choose something fresh in naïve therapy', on the front page of the leavepiece beneath a depiction of one apple at the end of four rows of oranges, implied that the use of Epivir plus Ziagen in treatment-naïve HIV patients was a 'new' alternative; 'fresh' was synonymous with 'new', 'recent' and 'latest'. Both Epivir and Ziagen had been available for many years for use in combination as part of a therapeutic regimen.

The Panel considered that, in combination with the visual, the majority of readers would assume that 'fresh' meant that there was an alternative option available for treatment-naïve patients to those commonly used. 'Fresh' did not necessarily imply that the option was new. The statement at issue did not contain the word 'new' and the Panel did not consider that the statement would be interpreted as such. No breach of the Code was ruled.

Gilead noted that the heading 'Choose Epivir + Ziagen an effective alternative NRTI backbone in naïve therapy' appeared on a page of the leavepiece which detailed the results of DeJesus *et al*. Two bullet points beneath the subheading 'The CNA 30024 study conclusions' read 'Equivalent virological response to Combivir*' and 'Significantly greater increase than Combivir* in median CD4+ count from baseline'. A footnote to each bullet point in small print at the bottom of the page stated 'Combivir given as its separate components lamivudine and zidovudine'. Gilead stated that, despite the footnote, the bullet points misleadingly implied that Combivir (a combination tablet containing lamivudine and zidovudine) had been used in DeJesus *et al*, whereas its components had been given separately.

The Panel noted that DeJesus *et al* compared Epivir plus Ziagen to lamivudine plus zidovudine, the constituents of Combivir. The Combivir summary of product characteristics (SPC) stated that when discontinuation of therapy with one of the active substances of Combivir or dose reduction was necessary separate preparations of lamivudine and zidovudine were available. It was recommended that separate preparations be administered to patients with renal or hepatic impairment and haematological adverse reactions. The SPC contained the warnings and precautions relevant to both lamivudine and zidovudine and stated that there were no additional precautions and warnings relevant to the combination Combivir. Section 5.1 stated that Combivir was shown to be bioequivalent to lamivudine 50mg and zidovudine 300mg given as separate tablets when administered to fasting subjects. The Panel also noted GlaxoSmithKline's submission of data regarding bioequivalence, clinical equivalence and tolerability.

The Panel considered that given the data and the statements in the Combivir SPC the two bullet points 'Equivalent virological response to Combivir' and 'Significantly greater increase than Combivir in median CD4+ count from baseline' were not misleading as alleged; no breach of the Code was ruled.

Gilead noted the claim 'Choose Epivir + Ziagen a backbone with established tolerability' had appeared as a heading to a page of the leavepiece which discussed DeJesus *et al* and featured two bullet points which favourably compared the tolerability of Epivir plus Ziagen with Combivir. A footnote to each bullet point, at the bottom of the page in small print, read 'Combivir given as its separate components lamivudine and zidovudine'. Gilead noted that once again two bullet points compared Epivir plus Ziagen with Combivir when in fact Combivir had been given as its separate components lamivudine and zidovudine.

The Panel considered that its comments above applied here. The Panel did not consider that either bullet point: 'Nausea and vomiting is 50% less common with Epivir + Ziagen than with Combivir' or 'Grade 3-4 neutropenia, anaemia, leukopenia and thrombocytopenia are significantly less common with Epivir + Ziagen than with Combivir (3% vs 7%)' was misleading as alleged. No breach of the Code was ruled.

Gilead alleged that the heading 'Choose Epivir + Ziagen to maximise subsequent therapy options', on a page which highlighted the effect of resistance mutations on the sensitivity of individual NRTIs, implied that by starting therapy with Epivir plus Ziagen patients were offered more alternatives than other combinations if therapy needed to be altered due to the development of resistance. Readers would assume that the claim meant that the Epivir/Ziagen combination offered the widest range of potential second-line therapy options of any combination that might be used in treatment-naïve therapy. Gilead alleged that the word 'maximise' was being used as a superlative, and that the claim that Epivir and Ziagen in combination maximised subsequent therapy options could not be substantiated.

Gilead also alleged that this broad claim was not supported by the references cited. The assessment of future options was best made on the basis of regimens proved to be clinically effective in the event of initial regimen failure. No clinical data was cited for the efficacy of Epivir plus Ziagen in patients who had failed their initial antiretroviral therapy. All the arguments provided were based on in-vitro resistance testing.

The Panel noted that one definition of maximize was 'increase to the highest possible degree; enhance to the utmost'. The Panel disagreed with GlaxoSmithKline's submission that the claim did not intimate that other regimens could not also

increase subsequent therapy options. The Panel considered that most readers would assume that the claim 'Choose Epivir + Ziagen to maximize subsequent therapy options' meant that by using Epivir plus Ziagen in treatment-naïve patients the prescriber would have more subsequent therapy options compared to any other combination treatment option and thus implied that Epivir plus Ziagen had some special merit; no evidence had been provided that this was so. The Panel thus ruled a breach of the Code.

The Panel further noted Gilead's submission that the assessment of further treatment options was best made on the basis of regimens proved to be clinically effective. The Panel noted GlaxoSmithKline's submission that *in vitro* testing was standard practice and was supported by the British HIV Association treatment guidelines which also stated that in medicine-naïve patients resistance testing prior to therapy might be of crucial value for a proportion of patients who carried mutations, especially in the context of demonstrable transmitted medicine resistance. Resistance testing was recommended for all medicine-naïve patients prior to commencing treatment. The Panel considered that it was important to assess not only the efficacy of HIV treatment options but also the loss of subsequent treatment options. In the absence of long-term clinical trial data showing the impact of mutations developed during first line therapy on subsequent therapy, *in vitro* resistant data would provide estimates of remaining options following treatment failure. The Panel thus did not consider that the claim 'Choose Epivir + Ziagen to maximize subsequent therapy options' was incapable of substantiation solely because the assessment of future therapy options was based on *in vitro* resistance testing as alleged and on this narrow point ruled no breach of the Code.

Gilead noted that a table entitled 'Effect of resistance mutations on the sensitivity of individual NRTIs' appeared beneath the headline claim at issue above and showed the sensitivity of M184V, K65R and M184V+K65R resistance mutations to the following medicines; ddI, ddC, AZT [zidovudine], d4T, ABC [Ziagen], TDF [tenofovir] and 3TC [Epivir]. The sensitivity data was obtained from PhenoSense reports for median phenotypes of these genotypic patterns. The heading to the table was referenced to Lanier *et al* (2003) and Nadler *et al* (2003).

Gilead alleged that in the context of the heading 'Choose Epivir + Ziagen to maximise subsequent therapy options', the table implied that the drug resistance mutuations which might develop as a result of treatment with Ziagen and Epivir were sensitive to subsequent therapy with other NRTIs. However, the table did not give a comprehensive list of possible mutations which might result from treatment with Ziagen. When the leavepiece was prepared, there was information available from a GlaxoSmithKline sponsored clinical study, Gazzard *et al* (2003), which showed that a regimen containing Epivir and Ziagen was associated with significant numbers of M184V and L74V resistant mutations (quoted as accounting for 48% and 26% of virological failures respectively). The SPC for Ziagen also listed the possible resistant mutation which might occur with treatment, and included M184V, L74V and Y115F; none of which were mentioned in the leavepiece at issue.

The significance of the M184V and L74V mutations was further emphasised by the conclusions of Lanier *et al* 'Mutational patterns involving (K)65R and/or (L)74V in conjunction with M184V are associated with resistance to multiple NRTSs', yet the table at issue did not refer to M184V and L74V, despite the fact that it was adapted from a similar table in Lanier *et al*. Gilead alleged that the data presented in the table was selective, and therefore neither balanced nor fair, and did not represent available evidence.

The Panel noted that the table at issue was referenced to Lanier *et al* and Nadler *et al*. Lanier *et al*, which featured a similar table to the one at issue, sought to predict NRTI options by assessing resistance data. Data for, *inter alia*, the L74V mutation in combination with M184V were presented. It was unclear whether the data related solely to treatment-naïve patients. The authors noted that in treatment-naïve patients any single mutation probably pre-existed therapy and double mutations might also be present. The authors concluded that K65R and/or 74V mutations in conjunction with M184V were associated with resistance to multiple NRTIs. These pathways required substantially fewer mutations to cause broad spectrum cross-resistance than thymidine analogue mutations. First line therapy should be chosen in part to minimize the potential for rapid selection of broadly cross-resistant mutants that might reduce future treatment options.

The Ziagen SPC, pharmacodynamic properties, identified Ziagen resistant mutations as M184V, K65R, L74V and Y115F. The Epivir SPC, pharmacodynamic properties, referred to the development of M184V mutation and explained that M184V mutants displayed greatly reduced susceptibility to Epivir. It mentioned that Ziagen maintained its retroviral activities against Epivir resistant HIV1 harbouring only the M184V mutation.

The Panel considered that this was a complex matter. The Panel noted its ruling above regarding the heading 'Choose Epivir and Ziagen to maximize therapy options'. The Panel considered that the table when viewed in light of the heading and subheading 'Effect of resistance mutations on the sensitivity of individual NRTIs' did not make the basis of the mutation selection sufficiently clear. There was an implication that the table listed all mutations that might develop during Ziagen and Epivir combination therapy and that was not so. The table was misleading in this regard. A breach of the Code was ruled.

Gilead noted that the section headed 'With virological failure on an Epivir + Ziagen backbone', which appeared on the same page as the claim and table at issue in the two previous points above,

featured two bullet points, 'The incidence of K65R ranges from 0 to < 1%' and 'The mutation most commonly seen is M184V alone'.

Gilead noted that, as explained above, Gazzard *et al* and Lanier *et al* clearly highlighted the significance of both the M184V and L74V mutations. This had again been ignored in the summary. Gilead alleged that the data presented was selective and therefore neither balanced nor fair, nor representative of all the evidence available in breach of the Code.

The Panel considered that its comments above were relevant. The bullet points now at issue were different to the data presented in the table; the subheading did not imply that the subsequent bullet points would discuss each mutation which would develop on Epivir/Ziagen combination therapy. The Panel thus did not consider the section headed 'With virological failure on an Epivir and Ziagen backbone' misleading as alleged. No breach of the Code was ruled.

Gilead Sciences Limited complained about a six page, gate-folded leavepiece for Epivir (lamivudine) and Ziagen (abacavir) entitled 'Oranges are not the only fruit. Choose something fresh in naïve therapy', which was produced by GlaxoSmithKline UK Limited. The leavepiece promoted Epivir plus Ziagen as an effective alternative nucleoside reverse transcriptase inhibitor (NRTI) backbone in treatment-naïve HIV patients.

The leavepiece was left with doctors following a detail from HIV representatives and had been so used since October 2003.

Gilead supplied two NRTIs, Viread (tenofovir) and Emtriva (emtricitabine).

1 Statement 'Oranges are not the only fruit. Choose something fresh in naïve therapy'

This statement appeared on the front page of the leavepiece beneath a depiction of one apple at the end of four rows of oranges.

COMPLAINT

Gilead alleged that this statement implied that the use of Epivir plus Ziagen in treatment-naïve HIV patients was a 'new' alternative and noted that the Oxford Thesaurus (1991 Edition) described 'fresh' with such synonyms as 'new', 'recent' and 'latest'. Both Epivir and Ziagen had been available for many years for use in combination as part of a therapeutic regimen. Gilead alleged a breach of Clause 7.11 of the Code.

RESPONSE

GlaxoSmithKline explained that in the UK, the majority of treatment-naïve HIV patients started anti-retroviral therapy (ART) on a regimen consisting of an NRTI backbone of lamivudine and zidovudine, plus a third agent. This third agent was usually a non-nucleoside reverse transcriptase inhibitor (NNRTI), although it might be a protease inhibitor (PI) or a third NRTI. In clinical practice, lamivudine plus zidovudine did not suit every patient, so alternative NRTI backbones needed to be considered in these cases.

Clinical trial data had previously illustrated the effectiveness of Epivir and Ziagen in combination with a PI, however, limited data existed on the efficacy and safety of Epivir plus Ziagen in combination with efavirenz – an NNRTI which was the current UK standard of care third agent used in ART.

DeJesus *et al* (2003) (study CNA 30024), was a large randomised, double-blind, placebo-controlled, multi-centre study to evaluate the efficacy and safety of an Epivir and Ziagen NRTI backbone compared to a lamivudine and zidovudine NRTI backbone, both in combination with efavirenz, in over 600 treatment-naïve adults. The results provided clinical data supporting the non-inferiority of Epivir plus Ziagen as an NRTI backbone compared to the current most widely used NRTI backbone, lamivudine and zidovudine. GlaxoSmithKline thus considered that the term 'fresh' was appropriate, in keeping with the fruit visuals used in the leavepiece, to inform readers of this recent clinical data supporting the use of an Epivir plus Ziagen NRTI backbone in treatment-naïve patients.

The Collins English Dictionary defined 'fresh' as: 'not stale or deteriorated; newly made, harvested etc', 'newly acquired, created, found etc.: fresh publications'. There was no intention to use the term 'fresh' as a synonym for 'new', but rather to emphasis the new evidence base for an alternative approach in treatment-naïve HIV patients, for whom the current standard of care was not appropriate. GlaxoSmithKline strongly refuted any suggestion of an intent to do so, and submitted therefore that there was no breach of Clause 7.11.

PANEL RULING

The Panel noted the parties' submissions on the various interpretations of 'fresh'. The Panel considered that in combination with the visual on the front page of the leavepiece the majority of readers would assume that 'fresh' meant that there was an alternative option available for treatment-naïve patients to those commonly used. 'Fresh' did not necessarily imply that the option was new.

The Panel noted that Clause 7.11 prohibited the use of the word 'new' to describe a product or presentation which had been generally available or therapeutic indication which had been generally promoted for more than twelve months in the UK. The Panel noted that the statement at issue did not contain the word 'new' and did not consider that the statement would be interpreted as such. The Panel thus ruled no breach of Clause 7.11 of the Code.

2 Page headed 'Choose Epivir + Ziagen an effective alternative NRTI backbone in naïve therapy'

This statement appeared as a heading to page 2 of the leavepiece which detailed the results of DeJesus *et al*.

Two bullet points beneath the subheading 'The CNA 30024 study conclusions' read 'Equivalent virological

response to Combivir*' and 'Significantly greater increase than Combivir* in median CD4+ count from baseline'. A footnote to each bullet point in small print at the bottom of the page read 'Combivir given as its separate components lamivudine and zidovudine' and that Epivir and Ziagen was given in combination with efavirenz as was Combivir.

COMPLAINT

Gilead noted that the two bullet points were referenced to DeJesus *et al* which compared a regimen of Epivir and Ziagen to lamivudine and zidovudine and not to Combivir (a combination tablet containing lamivudine and zidovudine) as stated in the piece. Despite the footnote stating that Combivir was given as its separate components, Gilead alleged that the bullet points misled by implication in breach of Clause 7.2.

RESPONSE

GlaxoSmithKline explained that Combivir was a fixed-dose combination of lamivudine 150mg and zidovudine 300mg licensed to be administered as one tablet twice daily. The separate components of Combivir were also available as Epivir (lamivudine) and Retrovir (zidovudine), respectively. Epivir was licensed to be administered as 300mg daily either as 300mg once daily or 150mg twice daily, and Retrovir as 500-600mg daily given in 2–3 divided doses (the usual adult dose being 300mg twice daily).

There was extensive data demonstrating the efficacy and safety of the lamivudine/zidovudine NRTI backbone as a constituent of a HAART (highly active anti-retroviral therapy) regimen – as well as data demonstrating the bioequivalence of Combivir to its separate components.

Moore *et al* (1999) had shown that Combivir was bioequivalent to co-administration of lamivudine and zidovudine separately. Eron *et al* (2000) had shown the antiretroviral activity of the fixed-dose formulation of lamivudine/zidovudine (Combivir) to be clinically equivalent to the conventional lamivudine and zidovudine regimen. There were no differences in medicine-related adverse events between the two arms. Eron *et al* also confirmed the findings of Rozenbaum and Chauveau (1998), which showed that Combivir taken twice daily had an equivalent safety profile to that of lamivudine (150mg bid) plus zidovudine (200mg tid).

In view of the well-known interchangeability and bioequivalence of Combivir and its components, GlaxoSmithKline submitted that the statements made on page 2 were not designed to mislead by implication. A footnote clearly stated that Combivir was administered as its separate components in DeJesus *et al* and provided additional clarifying information. GlaxoSmithKline submitted that the bullet points were reasonable and therefore there was no breach of Clause 7.2.

PANEL RULING

The Panel noted that DeJesus *et al* compared Epivir plus Ziagen to lamivudine plus zidovudine, the constituents of Combivir.

The Combivir summary of product characteristics (SPC) stated that when discontinuation of therapy with one of the active substances of Combivir or dose reduction was necessary separate preparations of lamivudine and zidovudine were available. The SPC recommended that separate preparations be administered to patients with renal or hepatic impairment and haematological adverse reactions. Section 4.4 of the SPC contained the warnings and precautions relevant to both lamivudine and zidovudine and stated that there were no additional precautions and warnings relevant to the combination Combivir. Section 5.1 of the SPC, Pharmacokinetics properties, stated that Combivir was shown to be bioequivalent to lamivudine 50mg and zidovudine 300mg given as separate tablets when administered to fasting subjects. The Panel also noted GlaxoSmithKline's submission regarding bioequivalence, clinical equivalence and tolerability studies; Moore *et al*, Eron *et al*.

The Panel considered that given the data and the statements in the Combivir SPC the two bullet points 'Equivalent virological response to Combivir' and 'Significantly greater increase than Combivir in median CD4+ count from baseline' were not misleading as alleged; no breach of Clause 7.2 was ruled.

3 Page headed 'Choose Epivir + Ziagen a backbone with established tolerability'

This claim appeared as a heading to page 5 of the leavepiece which discussed DeJesus *et al* (2003) and featured two bullet points which favourably compared the tolerability of Epivir plus Ziagen with Combivir. A footnote to each bullet point, at the bottom of the page in small print read 'Combivir given as its separate components lamivudine and zidovudine'.

COMPLAINT

Gilead noted that similar misleading statements to those at issue at point 2 above were also made on this page. Once again, two bullet points compared Epivir plus Ziagen with Combivir when in fact Combivir had been given as its separate components lamivudine and zidovudine. A breach of Clause 7.2 was alleged.

RESPONSE

GlaxoSmithKline referred to its comments at point 2 above.

PANEL RULING

The Panel considered that its comments at point 2 above applied here. The Panel did not consider that either bullet point: 'Nausea and vomiting is 50% less common with Epivir + Ziagen than with Combivir' or 'Grade 3-4 neutropenia, anaemia, leukopenia and thrombocytopenia are significantly less common with Epivir + Ziagen than with Combivir (3% vs 7%)' was

misleading as alleged. No breach of Clause 7.2 was ruled.

4 Claim 'Choose Epivir + Ziagen to maximise subsequent therapy options'

This claim headed page 3 which highlighted the effect of resistance mutations on the sensitivity of individual NRTIs.

COMPLAINT

Gilead stated that this claim implied that by starting therapy with a combination of Epivir and Ziagen, patients were offered more alternatives than other combinations if therapy needed to be altered due to the development of resistance.

Readers would assume that the claim meant that the Epivir and Ziagen combination offered the widest range of potential second-line therapy options of any medicine combination that might be used in treatment-naïve therapy. Consequently, the word 'maximise' was being used as a superlative. Gilead further alleged that the claim that Epivir and Ziagen in combination maximised subsequent therapy options could not be substantiated in breach of Clause 7.10.

Gilead also alleged that this broad claim was not supported by the references quoted. The assessment of future options was best made on the basis of regimens proved to be clinically effective in the event of initial regimen failure. No clinical data was referenced for the efficacy of Epivir plus Ziagen in patients shown to have failed their initial antiretroviral therapy. All the arguments provided were based on in-vitro resistance testing. Gilead alleged a breach of Clause 7.4 of the Code.

RESPONSE

GlaxoSmithKline did not accept that 'maximise' was being used as a superlative as there was no intimation that other regimens could not also increase subsequent therapy options. It did not accept that there had been a breach of Clause 7.10.

GlaxoSmithKline explained that in clinical practice, virological failure arose as a consequence of development of resistant mutations. During development it was therefore important to characterise those mutations associated with a particular medicine. Virologists conducted a series of *in vitro* experiments where wild type virus was cultured with increasing concentrations of a new medicine in an attempt to drive the development of these mutations, which could then be characterised. From this data phenotypic resistance data could be developed which would suggest when the efficacy of a medicine might be impacted by certain mutations.

Whilst it might be optimal to use clinical data to inform future treatment options following the virological failure of a HAART regimen, it was not always possible to do so. In the absence of such data it was disingenuous to state that the use of *in vitro* phenotypic and genotypic resistance testing to help predict the viral response of patients was not a valid and widely used methodology. Furthermore, as data became available from clinical trials it was often seen that when virological failure occurred the mutations that developed *in vivo* were similar to those that developed *in vitro*, although some mutations might occur more commonly than others. The use of *in vitro* resistance testing was standard practice and was further supported by the current HIV treatment guidelines issued by The British HIV Association (BHIVA). In a section of the guidelines which dealt with which medicines to use following failure of initial therapy it was stated: 'Wherever possible one or two different drugs of the NRTI/PI/NNRTI classes should be included in such a switch regimen. Resistance testing should be used to inform the choice of regimen, particularly for those with prior experience of NAs and PIs or NNRTIs. Patients whose therapy fails with adherence problems may benefit from simpler but effective regimens to which their virus is still sensitive'.

GlaxoSmithKline submitted that, for the intended audience of HIV clinicians, it was not misleading to use the results of phenotypic and genotypic resistance testing to substantiate the claims made, and therefore there was no breach of Clause 7.4.

PANEL RULING

The Panel noted that Clause 7.10 prohibited the use of superlatives except for those limited circumstances where they related to a clear fact about a medicine. Claims should not imply that a medicine had some special merit, quality or property unless this could be substantiated.

The Panel noted that maximize was defined, *inter alia*, as 'increase to the highest possible degree; enhance to the utmost' (ref New Shorter Oxford English Dictionary (1993)).

The Panel disagreed with GlaxoSmithKline's submission that the claim did not intimate that other regimens could not also increase subsequent therapy options. The Panel considered that most readers would assume that the claim 'Choose Epivir + Ziagen to maximize subsequent therapy options' meant that by using Epivir and Ziagen in combination in treatment-naïve patients the prescriber would have more subsequent therapy options compared to any other combination treatment option and thus implied that Epivir plus Ziagen had some special merit; no evidence had been provided that this was so. The Panel thus ruled a breach of Clause 7.10.

The Panel further noted Gilead's submission that the assessment of further treatment options was best made on the basis of regimens proved to be clinically effective. The Panel noted GlaxoSmithKline's submission that *in vitro* testing was standard practice and was supported by the BHIVA treatment guidelines which also stated that in medicine-naïve patients resistance testing prior to therapy might be of crucial value for a proportion of patients who carried mutations, especially in the context of demonstrable transmitted medicine resistance. Resistance testing was recommended for all medicine-naïve patients prior to commencing treatment. The Panel considered

that it was important to assess not only the efficacy of HIV treatment options but also the loss of subsequent treatment options. In the absence of long-term clinical trial data showing the impact of mutations developed during first line therapy on subsequent therapy, *in vitro* resistant data would provide estimates of remaining options following treatment failure. The Panel thus did not consider that the claim 'Choose Epivir + Ziagen to maximize subsequent therapy options' was incapable of substantiation solely because the assessment of future therapy options was based on *in vitro* resistance testing as alleged and on this narrow point ruled no breach of Clause 7.4 of the Code.

5 Table entitled 'Effect of resistance mutations on the sensitivity of individual NRTIs'

This table appeared beneath the headline claim at issue at point 4 above and showed the sensitivity of M184V, K65R and M184V+K65R resistance mutations to the following medicines; ddI, ddC, AZT [zidovudine], d4T, ABC [Ziagen], TDF [tenofovir] and 3TC [Epivir]. The sensitivity data was obtained from PhenoSense reports for median phenotypes of these genotypic patterns. The heading to the table was referenced to Lanier *et al* (2003) and Nadler *et al* (2003).

COMPLAINT

Gilead alleged that in the context of the heading 'Choose Epivir + Ziagen to maximise subsequent therapy options', the table implied that the drug resistance mutuations which might develop as a result of treatment with Ziagen and Epivir were sensitive to subsequent therapy with other NRTIs. However, the table did not give a comprehensive list of possible mutations which might result from treatment with Ziagen. When the leavepiece was prepared (15 September 2003), there was information available from a GlaxoSmithKline sponsored clinical study, Gazzard *et al* 2003 (the ZODIAC study), which showed that a regimen containing Epivir and Ziagen was associated with significant numbers of M184V and L74V resistant mutations (quoted as accounting for 48% and 26% of virological failures respectively). The SPC for Ziagen (18 March 2004) also listed the possible resistant mutation which might occur with treatment, and included M184V, L74V and Y115F; none of which were mentioned in the leavepiece at issue.

The significance of the M184V and L74V mutations was further emphasised by the conclusions from a poster by Lanier *et al* which stated: 'Mutational patterns involving (K)65R and/or (L)74V in conjunction with M184V are associated with resistance to multiple NRTSs', and yet, the table at issue made no reference of M184V and L74V, despite the fact that it was adapted from a similar table (table 2) in the Lanier poster.

The data presented in the table at issue was selective and therefore neither balanced nor fair, nor representative of all the evidence available. Gilead alleged a breach of Clause 7.2 of the Code.

RESPONSE

GlaxoSmithKline disagreed with Gilead's statement that the table implied that the drug resistance mutations which might develop as a result of treatment with Ziagen plus Epivir were sensitive to subsequent therapy with other NRTIs. The table clearly illustrated that virus was not sensitive to Epivir in the presence of the M184V mutation alone, and that virus was not sensitive to ddI, ddC, tenofovir and Epivir in the presence of the K65R mutation alone, and that virus was not sensitive to ddI, ddC, or Epivir in the presence of the M184V + K65R mutations. The table illustrated that virus might be partially sensitive to Ziagen and tenofovir in the presence of the M184V + K65R mutations.

PhenoSense was a virological database widely used by laboratories to provide clinical guidance to physicians for the selection of new agents when the patient's regimen had failed due to resistance mutations.

The table in question made no claim to be a comprehensive listing of the effects of all resistance mutations on all NRTIs. The mutations chosen were those of particular interest (because they occurred in the greatest numbers) when considering the studies in question and cited in the leavepiece – namely for tenofovir, Miller *et al* (2002) and for Epivir/Ziagen, DeJesus *et al*.

GlaxoSmithKline noted Gilead's comment regarding the lack of data presented for the L74V resistance mutation. When the leavepiece was prepared none of the data available for DeJesus *et al* noted the development of the L74V mutation. More recently available data from a poster presentation, Irlbeck *et al* (2004), noted that the L74V mutation was subsequently found to have developed in one subject 12 weeks after failure with the M184V and G190S mutations. Even at this later time point, no cases of the K65R mutation were found to have developed.

GlaxoSmithKline summarised virology results for the cited studies DeJesus *et al* and Miller *et al* which investigated the use of either Ziagen or tenofovir (Viread) in combination with Epivir and efavirenz (Sustiva).

GlaxoSmithKline noted that genotypic typing of the HIV virus in subjects experiencing virological failure enabled the presence or absence of specific virological mutations to be confirmed. Definitions of what constituted virological failure could vary from trial to trial – in DeJesus *et al* it was based on a new FDA requirement; the time to loss of virological response algorithm, which defined virological failure as either:

- ***Rebound:*** Confirmed two consecutive plasma HIV-1 RNA values greater than the lower limit of quantification (50copies/ml) after achieving a confirmed level of <50copies/ml during the treatment phase
- ***Never Suppressed:*** Plasma HIV-1 RNA levels never achieve confirmed suppression (<50copies/ml) with at least 48 weeks of randomised treatment
- ***Insufficient Virological Response:*** Plasma HIV-1 RNA levels never achieving confirmed

suppression (<50copies/ml) and investigator identified the reason for treatment discontinuation prior to week 48 due to insufficient viral load response.

Miller *et al* defined it as patients with >400copies/ml of HIV-1 RNA at week 48, week 96 or at early discontinuation for any reason.

It was possible for patients to be defined as failing virologically and yet to have a viral load that was still too low to enable genotypic analysis to be successfully performed with current techniques – this was the case for some subjects in DeJesus *et al*. For this reason the data was presented as the number of cases of each specific mutation as a percentage of the number that could be genotyped successfully.

Of the 33 virological failures observed in DeJesus *et al*, 20 were seen in the Epivir/Ziagen/efavirenz arm and 13 in the zidovudine/lamivudine/efavirenz arm, with genotyping available for 16 of 33 virological failures. The reason for this was that there was difficulty in establishing genotype for those virological failures with plasma HIV-1 levels <200copies/ml.

Of the 16 subjects with genotype available, 8 subjects demonstrated wild type virus (suggesting poor adherence to treatment rather than lack of efficacy of the ART regimen) and 8 had mutant virus. In the Epivir/Ziagen/efavirenz arm, 6 subjects had wild type virus and 4 had mutant virus (all 4 had NNRTI associated mutations and two also had M184V and M184I). In the zidovudine/lamivudine/efavirenz arm, 2 subjects had wild type virus and 4 mutant virus (all had NNRTI associated mutations and M184V). No subjects were demonstrated to have the L74V or K65R mutation at time of failure.

GlaxoSmithKline did not understand why Gilead had referred to the ZODIAC study since this study included Ziagen being administered in a once daily regimen. Ziagen was currently licensed for twice daily administration only, and it would be inappropriate to include data supporting an unlicensed dosage schedule in promotional material. Gilead's repeated references in its letter to studies using Ziagen in a once daily regimen were therefore misleading and irrelevant.

However, for completeness and as background information GlaxoSmithKline provided a table which summarized the virology results for the ZODIAC study, which investigated the use of Ziagen in a once daily or twice daily regimen in combination with Epivir and efavirenz.

In the ZODIAC study there was a slightly higher incidence of the L74V mutation than in DeJesus *et al*. Upon examination of those subjects experiencing virological failure (that could be genotyped), 23% were found to have already possessed virological mutations at baseline, which might have impacted on the subsequent mutation selection process.

If GlaxoSmithKline had chosen to include a wider range of clinical studies, where an Epivir/Ziagen NRTI backbone (at currently licensed doses) had been studied in treatment-naïve HIV patients, this would have further supported the company's premise that M184V was the most commonly produced NRTI associated mutation following therapy with these medicines. However, as Miller *et al* was currently the only published study where a tenofovir/Epivir backbone had been used in treatment-naïve patients, GlaxoSmithKline considered that a comparison of these two large similarly designed trials (Miller *et al* and DeJesus *et al*) provided the most balanced range of data.

In the leavepiece at issue, virological data for the Miller *et al* study at 48 weeks was used, but GlaxoSmithKline for completeness provided 96 week data (Miller *et al* 2002 and Miller *et al* 2003).

GlaxoSmithKline provided a copy of an extract from The Stanford HIV Drug Resistance Database, an independent and internationally respected database, which showed that the impact of the K65R mutation on subsequent NRTI treatment options was much greater than that of the L74V and Y115F mutations. Following virological failure with the K65R mutation, only ziclovudine was left fully sensitive. Following failure with Y115F, all nucleosides except Ziagen remained fully sensitive. Following failure with L74V, zidovudine, d4T, kenofovir, FTC and Epivir remained.

In summary therefore, GlaxoSmithKline refuted that the data presented in the table at issue was selective and that there had been any breach of Clause 7.2.

PANEL RULING

The Panel noted Gilead's allegation that in the context of the heading 'Choose Epivir + Ziagen to maximize subsequent therapy options' the table implied that the drug resistance mutations which might develop as a result of treatment with Ziagen plus Epivir were sensitive to subsequent therapy with other NRTIs. Gilead alleged that the data presented was selective.

The Panel also noted GlaxoSmithKline's submission that the table did not purport to be a comprehensive listing of the effects of all resistance mutations on all NRTIs. The mutations chosen were those of particular interest because they were particularly prevalent in DeJesus *et al* and Miller *et al*. Miller *et al* was currently the only published study where a tenofovir/Epivir backbone had been used in treatment-naïve patients. GlaxoSmithKline thus submitted that a comparison of these similarly designed trials provided the most balanced range of data. The Panel noted GlaxoSmithKline's comments upon the studies' design and results.

The Panel noted GlaxoSmithKline's submission that when the leavepiece was prepared the available data for DeJesus *et al* did not mention the L74V mutation. The Panel noted that material had to comply with the Code not only when it was prepared but also throughout the period when it was used.

The table at issue was referenced to Lanier *et al* (2003) and Nadler *et al* (2003). Lanier *et al*, which featured a similar table to the one at issue, sought to predict NRTI options by assessing resistance data. Data for, *inter alia*, the L74V mutation in combination with M184V were presented. It was unclear whether the data related solely to treatment-naïve patients. The authors noted that in treatment-naïve patients any single mutation probably pre-existed therapy and

double mutations might also be present. The authors concluded that K65R and/or 74V mutations in conjunction with M184V were associated with resistance to multiple NRTIs. These pathways required substantially fewer mutations to cause broad spectrum cross-resistance than thymidine analogue mutations. First line therapy should be chosen in part to minimize the potential for rapid selection of broadly cross-resistant mutants that might reduce future treatment options.

The Ziagen SPC, pharmacodynamic properties identified Ziagen resistant mutations as M184V, K65R, L74V and Y115F. The Epivir SPC, pharmacodynamic properties referred to the development of M184V mutation and explained that M184V mutants displayed greatly reduced susceptibility to Epivir. It mentioned that Ziagen maintained its retroviral activities against Epivir resistant HIV1 harbouring only the M184V mutation.

The Panel considered that this was a complex matter. The Panel noted its ruling at point 4 above regarding the heading 'Choose Epivir and Ziagen to maximize therapy options'. The Panel considered that the table when viewed in light of the heading and subheading 'Effect of resistance mutations on the sensitivity of individual NRTIs' did not make the basis of the mutation selection sufficiently clear. There was an implication that the table listed all mutations that might develop during Ziagen and Epivir combination therapy and that was not so. The table was misleading in this regard. A breach of Clause 7.2 was ruled.

6 Section headed 'With virological failure on an Epivir + Ziagen backbone:'

This section, which appeared on page 3, the same page as the claim and table at issue at points 4 and 5 above, featured two bullet points which read 'The incidence of K65R ranges from 0 to < 1%' and 'The mutation most commonly seen is M184V alone'.

COMPLAINT

Gilead noted that, as explained above, the ZODIAC study and Lanier *et al* clearly highlighted the significance of both the M184V and L74V mutations. This had again been ignored in the summary. Gilead alleged that the data presented was selective and therefore neither balanced nor fair, nor representative of all the evidence available in breach of Clause 7.2 of the Code.

RESPONSE

GlaxoSmithKline noted that Gilead appeared to have based its argument on data referring to Ziagen use in an unlicensed dosage schedule, and again, this was irrelevant.

With regard to the L74V mutation, the references cited gave the incidence of this mutation in studies with Ziagen administered at licensed doses as a percentage of those failing ranging from 0.9% to 5%. Based on information contained in The Stanford HIV Drug Resistance Database GlaxoSmithKline contended that, in terms of future NRTI sequencing options available, the consequences were less limiting than would be the case with the development of the K65R mutation. Thus, GlaxoSmithKline denied that the significance of the L74V mutation had been ignored.

With regard to the K65R mutation, the references cited gave the incidence of this mutation as a percentage of those failing ranging from 0% to 2.1%, which contrasted with the 22% incidence observed in Miller *et al*. Again, GlaxoSmithKline refuted that the significance of the K65R mutation had been ignored, and did not consider that there had been a breach of Clause 7.2.

PANEL RULING

The Panel considered that its comments at point 5 above were relevant. The Panel considered that the bullet points now at issue were different to the data presented in the table; the subheading did not imply that the subsequent bullet points would discuss each mutation which would develop on Epivir/Ziagen combination therapy. The Panel thus did not consider the section headed 'With virological failure on an Epivir and Ziagen backbone' misleading as alleged. No breach of Clause 7.2 was ruled.

Complaint received **20 May 2004**

Case completed **12 August 2004**

CASE AUTH/1594/6/04

ROCHE v NOVARTIS

Zometa detail aid

Roche complained about a Zometa (zoledronic acid) detail aid issued by Novartis. Zometa was licensed for the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone. It could also be used to treat tumour-induced hypercalcaemia. Roche marketed Bondronat which was available as film coated tablets and as a concentrate for solution for intravenous administration. Both formulations were indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. In addition, Bondronat IV was also indicated for the treatment of tumour-induced hypercalcaemia with or without metastases. Zometa and Bondronat were bisphosphonates.

Roche stated that the headline claim 'Licensed for bone metastases in more tumour types than any other bisphosphonate' on the front cover of the detail aid did not specify that the product was licensed for the prevention of skeletal related events in patients with advanced malignancies involving bone. Zometa was not licensed to prevent or clear bone metastases as this claim suggested. Roche alleged that the claim was misleading.

The Panel noted the licensed indication for Zometa and considered that the claim 'Licensed for bone metastases in more tumour types than any other bisphosphonate' was not sufficiently clear in this regard; there was an implication that the product could be used to treat the metastases *per se* and that was not so. The Panel considered that the claim was misleading. A breach of the Code was ruled. This ruling was appealed.

On appeal by Novartis, the Appeal Board, although noting that Zometa would have an effect on bone metastases and the product was licensed to prevent five specific skeletal related events in patients with advanced malignancies involving bone, nonetheless considered the claim was not sufficiently clear. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Roche alleged that the claim 'Broad protection from the threat of skeletal complications' which appeared as a strapline below the product logo on the front cover of the detail aid and also on other pages was all-embracing.

The Panel noted that the strapline and product logo, together with the claim at issue above, was all the promotional copy that appeared on page 1. The Panel noted its comments and ruling above and considered that, given the context in which it appeared, the claim now at issue, 'Broad protection from the threat of skeletal complications' was exaggerated and all-embracing; it reinforced the impression that Zometa could be used to treat the metastases *per se* or otherwise protect patients from developing bone metastases which was not so. A breach of the Code was ruled. This ruling was appealed.

Upon appeal by Novartis the Appeal Board considered that, given the context in which it appeared, the claim was exaggerated and all-embracing. The Appeal Board considered that the claim gave the impression that Zometa could provide protection from the formation of new metastases which was not so. Skeletal related events as referred to in the summary of product characteristics (SPC) was not the same as skeletal complications. The Appeal Board upheld the Panel's ruling of a breach of the Code.

With regard to other uses of the claim the Panel noted that the product logo and strapline also appeared at the bottom of pages 3, 8, 9, 12 and 14. Page 3 was part of a double-page spread headed 'Zometa – meeting the challenges of treating metastic bone disease' and included details of the most common skeletal related events in patients with metastatic bone disease. Pages 8 and 9 together were headed 'Zometa – a new standard for the treatment of hypercalcaemic cancer patients', page 12 dealt with the tolerability of Zometa and the prescribing information and references were given on page 14. The Panel considered that given the content of these pages the claim 'Broad protection from the threat of skeletal complications' was not unreasonable; there was no implication that Zometa prevented the patient developing metastases. The Panel considered that, other than on page 1 of the detail aid, given the context in which it appeared, the claim was not exaggerated or all-embracing. No breach of the Code was ruled.

Roche noted a bar chart on page 3 of the detail aid, adapted from Green *et al* (1994), depicted the potency of seven bisphosphonates relative to pamidronate disodium *in vivo* (hypercalcaemic rat) on a linear scale. Six of the seven medicines shown had a relative potency of less than 44. Of those six ibandronate (Bondronat) had the highest relative potency of 43.6. The relative potency of Zometa was given as 847.

Roche alleged that the bar chart misled, misrepresented and exaggerated the difference in potencies between Bondronat and Zometa. It was not possible to see how the bar chart had been generated from the cited reference. In addition, at the time the detail aid was produced Bondronat did not have a product licence for metastatic bone disease and, hence the medicine was promoted prior to the grant of its marketing authorization.

Roche stated that the footnote on the table of data below the chart stating that 'potency is not necessarily related to clinical efficacy' could not be used to ameliorate the impact of the clinical message at the claim 'Broad protection from the threat of skeletal complications'.

Roche stated that the use of the bar chart entitled 'Zometa – meeting the challenges of treating metastatic bone disease' and with a strapline – 'Broad protection from the threat of skeletal complications' misled the reader into unfairly assuming greater efficacy for Zometa than Bondronat when no such data existed.

The Panel considered that as the page was headed 'Zometa – meeting the challenges of treating metastatic bone disease', it would be viewed in terms of the clinical situation. Although the bar chart at issue showed that in terms of *in vivo* potency Zometa was many times more potent than the other bisphosphonates, given the context, some readers would assume that it also meant that Zometa was the most efficacious. The Panel further noted that although the page heading referred to metastatic bone disease the bar chart related to the treatment of hypercalcaemia. Overall the Panel considered that the bar chart was misleading and exaggerated the differences between Zometa and Bondronat as alleged. Breaches of the Code were ruled which were upheld on appeal from Novartis.

The Panel considered that although the bar chart referred to Roche's product ibondronate, regardless of what it was licensed for Novartis could not be accused of promoting it. No breach of the Code was ruled.

The Panel considered that the bar chart was misleading with regard to the implied relative efficacy of Bondronat and Zometa but considered that this was covered by its ruling above. The Panel did not, however, consider that the bar chart disparaged Bondronat. No breach of the Code was ruled.

Roche noted a table of data below the bar chart at issue above compared the relative potency (*in vivo*), infusion time, bioavailability and route of administration of Zometa, pamidronate and oral clodronate. It was noted that with oral preparations, patients had to adhere to a strict dosing schedule and that the potential for poor compliance and treatment failure was high.

Roche alleged that the omission of Bondronat from the table was unbalanced. Roche further noted that although comments were made about the posology of other bisphosphonates, no caution was discussed about Zometa and its use related to renal function (ie it could not be used in a patient with a creatinine clearance < 30ml/min and there were concerns over concomitant use with other potentially nephrotoxic agents).

The Panel noted that the leavepiece pre-dated Bondronat's licence for use in metastatic bone disease. The Panel thus ruled no breach of the Code with regard to the omission of Bondronat from the table.

The Panel noted that the table detailed relative potency (*in vivo*), infusion time (minutes), availability % and route of administration. None of these headings related to the use of the bisphosphonates in patients with impaired renal function. The Panel therefore did not consider that omission of such data was misleading. No breach of the Code was ruled.

Roche alleged that the claim 'Statistically significant effects were achieved at low concentration' which appeared beneath a statement that pre-clinical studies had shown significant effects of Zometa on cancer cells and its ability to interfere with the metastatic process in bone in animal models was all-embracing. Such effects were commonly seen with bisphosphonates and the page imputed special merit from pre-clinical data where there might be none.

The Panel noted that the page detailed Zometa's mode of action and featured a diagram showing that it mediated osteosclerotic bone formation and inhibited osteolytic bone resorption. The Panel did not consider, given the context in which it appeared, that the claim at issue, 'Statistically significant effects were achieved at low concentration' was exaggerated, all-embracing or that it implied special merit from pre-clinical data where there might be none. No breach of the Code was ruled.

Roche alleged that the headline claim 'Zometa – superior to pamidronate in reducing the risk of bone complications in advanced breast cancer' was all embracing; it implied that all patients with advanced breast cancer would benefit which not true. The data referred to a highly selected subset ie patients who were undergoing hormonal therapy and who had suffered from hypercalcaemia of malignancy. The data on file to support the claim consisted of four tables from a confidential report. The data had been supplied on request with a few hand scribbled calculations but without explanation. Roche alleged this failed to adequately substantiate the claim.

Roche added that apart from radiation to bone (a secondary endpoint), the original publication showed that the primary endpoint of non-inferiority was reached, ie Zometa was no worse than pamidronate (Rosen *et al* 2001). The SPC also stated 'Zometa 4mg showed comparable efficacy to 90mg pamidronate in the prevention of SREs [Skeletal Related Events]'. Although the SPC included a statement of benefit over pamidronate, this was based on a secondary endpoint of the trial. The claim that Zometa was superior to pamidronate was therefore not consistent with the SPC.

The Panel noted that the claim at issue 'Zometa – superior to pamidronate in reducing the risk of bone complications in advanced breast cancer' was referenced to data on file published as Rosen *et al* (2003) and Rosen *et al* (2004). The data did not, as submitted by Roche, refer only to those who were undergoing hormonal therapy. Rosen *et al* (2003) looked at the treatment of skeletal complications in patients with advanced multiple myeloma or breast cancer. Rosen *et al* (2004) looked at the treatment of bone metastases in breast cancer patients with at least one osteolytic lesion. Rosen *et al* (2003) stated that in patients with breast cancer Zometa 4mg was significantly more effective than pamidronate, reducing the risk of skeletal related events by an additional 20% (p=0.025) compared with pamidronate and by an additional 30% in patients receiving hormonal therapy (p=0.009).

Rosen *et al* (2004) stated that multiple-event analysis showed a 20% additional reduction in the risk of skeletal events (p=0.037) for Zometa-treated patients compared with those taking pamidronate. In patients with lytic lesions although the primary endpoint (the proportion of patients with a skeletal event) did not achieve statistical significance,

multiple-event analysis demonstrated that the benefit of Zometa was even greater compared with pamidronate with an additional 30% reduction in the risk of skeletal events, a secondary endpoint, being observed (p=0.01). The Panel noted that the discussion section of Rosen *et al* (2004) stated that the data strongly suggested that Zometa might be more effective clinically compared with pamidronate in patients with breast cancer and at least one osteolytic lesion and in the overall population of patients with breast carcinoma. Such caution was not reflected in the claim at issue. The Panel considered that the headline claim was not a fair reflection of the study results and was misleading and exaggerated in that regard. Breaches of the Code were ruled.

Upon appeal by Novartis the Appeal Board noted that the data from Rosen *et al* (2003) was a pre-planned, prospective analysis whereas Rosen *et al* (2004), was a *post-hoc* retrospective analysis of the data. The Appeal Board considered that the headline claim was a fair reflection of the data and as such was not misleading or exaggerated. No breach of the Code was ruled.

The Panel noted that at the time the claim was made the Rosen *et al* papers had not been published; only the four pages of data on file, which comprised tables showing hazard ratios, p values and robust p values for the various treatments were available. Some handwritten calculations were included on two of the tables. The Panel considered that the presentation of the data on file was such that it was difficult to understand and inadequate to substantiate the claim at issue. A breach of the Code was ruled.

The Panel noted that the Zometa SPC stated that in a combined patient group of those with multiple myeloma or breast cancer with at least one bone lesion, Zometa and pamidronate had comparable efficacy in prevention of skeletal related events. The claim at issue related only to patients with breast cancer. In that regard the Panel did not consider that the claim was inconsistent with the SPC. No breach of the Code was ruled.

The claim 'Zometa – effective bone protection in breast cancer' appeared below a chart which showed that breast cancer patients treated with Zometa had a 20% lower risk of developing skeletal complications compared with pamidronate. Roche noted that Zometa was not licensed for breast cancer *per se*, nor adjuvant use to prevent bone metastases, as this claim promoted. The data on file referred to above was supplied on request. There was no mention of bone pain scores. Roche alleged that the data did not substantiate the claim.

The Panel noted that the claim 'Zometa – effective bone protection in breast cancer' appeared on a page on which the heading referred to 'advanced breast cancer'. The page tag, however, stated 'Zometa – in breast cancer'. In that context the Panel considered that the claim implied that Zometa was authorized for use in all breast cancer patients which was not so. The claim was inconsistent with the SPC. The Panel ruled a breach of the Code as alleged.

Upon appeal by Novartis, the Appeal Board on balance considered that the claim at issue implied that Zometa was authorized for use in all breast cancer patients which was not so. The claim was thus inconsistent with the SPC. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Roche noted that the claim 'Zometa consistently reduces the incidences of all types of skeletal-related events (SREs)' and associated bar chart were referenced to the data on file referred to above. The bar chart showed numerical values for Zometa versus pamidronate in terms of the percentage of patients with fracture (all types), radiation to bone, surgery to bone and spinal cord compression. Apart from radiation to bone (a secondary end point), the primary end point showed non-inferiority, ie Zometa was no worse than pamidronate. The SPC also stated 'Zometa 4mg showed comparable efficacy to 90mg pamidronate in the prevention of SREs'. In the absence of values of significance on the bar chart, the reader could not evaluate this claim, which was misleading and all-embracing.

The Panel noted that the statement in the SPC that Zometa was comparable to pamidronate in the prevention of skeletal related events referred to a study of patients with multiple myeloma or breast cancer with at least one bone lesion. The bar chart showed only the breast cancer data and that, compared with pamidronate, Zometa reduced the percentage of patients with each skeletal related event. The clinical significance of the difference between the two medicines was not mentioned. The Panel considered that the claim and the bar chart were misleading; a breach of the Code was ruled. The Panel also considered that the claim was all-embracing. A breach of the Code was ruled. These rulings were appealed.

Upon appeal by Novartis the Appeal Board noted that although the claim at issue referred to all skeletal related events the incidence of tumour related hypercalcaemia was not shown on the bar chart. Although there was a numerical advantage for Zometa with regard to each skeletal related event there was no indication as to the statistical significance of any of the data; all of the advantages shown for Zometa could thus have been chance findings. The Appeal Board considered that the claim was misleading and all-embracing as alleged. The Panel's rulings of breaches of the Code were upheld.

Roche drew attention to a claim 'Consistently lower pain scores reported throughout the study' and associated bar chart which showed eight study periods over the 24 months of the study. Bone pain scores were statistically significantly different to placebo at only half of those study periods and, even then, the actual 'p' number was not given – just 'p<0.05'. Roche alleged that the claim was misleading and all-embracing.

The Panel noted that the visual impression of the bar chart was that at every time point Zometa-treated patients had lower pain scores than those treated with placebo and that such differences were meaningful. This was not so. At months 6, 12, 15

and 18, although there was a trend to a lower pain score with Zometa, the results were not statistically significant. The Panel did not consider that use of the word 'consistently' served to negate the otherwise misleading impression. A breach of the Code was ruled. The Panel ruled that the claim was all-embracing in breach of the Code. This ruling was appealed.

Upon appeal by Novartis the Appeal Board noted that the claim was based on a long-term study which had shown a difference in pain scores for Zometa and placebo. Although only four of the eight time points were statistically significant, these were clearly marked and a p value given. By default there must have been no statistically significant differences at the other time points. The Appeal Board considered that the bar chart was clear and was not misleading and no breach of the Code was ruled. The Appeal Board did not consider that the claim was all-embracing. No breach of the Code was ruled.

Roche alleged a breach of the Code with regard to the use of the word 'new' in the claim 'Zometa – a new standard for the treatment of hypercalcaemic cancer patients' as Zometa was launched more than 12 months ago. Roche also alleged that the claim was all-embracing as it suggested Zometa could be used to treat any cause of hypercalcaemia in cancer whereas it was only licensed for 'tumour-induced' hypercalcaemia. There were other causes of hypercalcaemia and although it was highly likely that a patient's hypercalcaemia was due to their malignancy, it was not automatically the case. This claim was therefore all-embracing and outside of the marketing authorization.

The Panel noted that in the claim at issue 'new' was used to describe the standard of care, not Zometa thus the Panel ruled no breach of the Code.

The Panel noted that, in cancer patients, hypercalcaemia was likely to be tumour-induced as opposed to due to any other cause. The page tags read 'Zometa-tumour induced hypercalcaemia'. The Panel thus did not consider the claim 'Zometa – a new standard for the treatment of hypercalcaemic cancer patients' was all-embracing. No breach of the Code was ruled. The claim did not promote Zometa for an unlicensed indication and thus no breach was ruled.

Roche alleged that the claim 'Zometa decreases the risk of a skeletal complication in multiple myeloma compared to pamidronate' was misleading. The claim was referenced to Rosen *et al* (2001). This was followed by a chart showing the relative risk of Zometa versus pamidronate in multiple myeloma. The p value was p=0.593. The claim implied an advantage for Zometa whereas there was no significant difference between it and pamidronate.

The Panel noted that, there was no statistically significant difference between Zometa and pamidronate. The Panel considered that the claim was misleading as alleged. A breach of the Code was ruled which was upheld on appeal by Novartis.

Roche stated that the claim 'Zometa has superior efficacy to pamidronate disodium in hypercalcaemic cancer patients' implied that all hypercalcaemic cancer patients would benefit. The data (Major *et al* 2001) only referred to breast cancer patients who were undergoing hormonal therapy and who had suffered from hypercalcaemia of malignancy – a highly selected subset. Also, as noted above, not all hypercalcaemic cancer patients would have tumour-induced hypercalcaemia. Roche alleged that the claim was all-embracing and not true.

The Panel noted that Major *et al*, recruited patients ≥ 18 years of age with histological or cytological confirmation of cancer and severe hypercalcaemia of malignancy. Patients were not limited to those with breast cancer undergoing hormonal therapy as alleged; patients had a wide range of primary cancer sites. The Panel noted its comments above that, in patients with cancer, hypercalcaemia was likely to be tumour-induced as opposed to due to any other cause. The Panel considered that, in the context in which it appeared, ie on a page summarising all that had gone before, the claim was not misleading or all-embracing as alleged. No breach of the Code were ruled.

Roche noted the claim 'Zometa is quick and convenient to deliver', referenced to the Zometa SPC, and alleged that 'quick' was not a medical term; it was vague and without substantiation. 'Quick' did not appear in the SPC. It also misled the reader as patients required a pre-dose renal test as, according to the SPC Zometa was not recommended in patients with severe renal failure and the dose should be withheld if renal function has deteriorated. A 15 minute infusion was not 'quick' and the claim was thus misleading.

Roche noted that the patient must usually: attend hospital as an out patient, have bloods taken to check renal function, have a vein cannulated and an infusion given, have medical and nursing attendance, have the intravenous line taken down and be checked to ensure they could safely be sent home. The whole process could not be described as 'convenient' especially when the only reason to visit hospital was to receive a bisphosphonate. Intravenous care at home also carried difficulties and risks. Roche alleged that the claim was misleading.

The Panel noted that, the claim at issue appeared on a page which summarized the Zometa data and compared it with other bisphosphonates. The claim 'Zometa is quick and convenient to administer' would be read in that context.

Compared with Bondronat or Aredia, Zometa could be infused in smaller volumes over a shorter period of time. The Panel thus considered that Zometa could be administered quickly. No breach of the Code was ruled in that regard.

The Panel considered that the claim that Zometa was convenient to use implied an advantage over other similar therapies. This was not so. As with other intravenous bisphosphonates, patients had to have their renal function and plasma electrolytes measured. Prescribers must also ensure that patients treated with Zometa were adequately hydrated. This was not the case for other

bisphosphonates. The Panel considered that Zometa was no more convenient to administer than other bisphosphonates and in that regard the implied advantage was misleading. A breach of the Code was ruled.

Upon appeal by Novartis the Appeal Board did not consider that, within the overall context of treating a patient with cancer, Zometa would be seen as inconvenient. Zometa could be administered by a 15 minute infusion, which was faster than other IV bisphosphonates. The Appeal Board considered that this advantage was in itself a convenient aspect of Zometa therapy. The Appeal Board did not consider that the claim was misleading and no breach of the Code was ruled.

Roche noted the claim 'Zometa is well tolerated' and stated that of all the issues raised by the detail aid, the fact that Novartis had not fully informed prescibers about the issues surrounding Zometa and renal toxicity was of greatest concern. Renal toxicity was described as 'common' in the Zometa SPC and yet was not even mentioned in the detail aid which gave prominence to details only of efficacy.

References were not made to the letter to the New England Journal of Medicine (Chang *et al* 2003) from the Food and Drug Administration (FDA) discussing renal toxicity concerns about zoledronic acid. Roche noted that no such concerns were raised in this letter about any other bisphosphonates. Other publications had referred to Zometa's renal toxicity (Markowitz *et al* 2003 and Johnson *et al* 2003).

No reference was made to the important safety requirement of withholding Zometa treatment in patients with severe renal impairment. The obligation to discontinue therapy put the patient at further risk of skeletal events in the absence of bisphosphonate cover from Zometa. No mention was made of the need for caution with the use of Zometa with other potentially nephrotoxic agents. Roche alleged that Novartis had failed to give due emphasis to these important safety matters when discussing safety issues and this might be serious enough to constitute a breach of Clause 2.

The Panel noted that the Zometa SPC stated that the product must only be used by clinicians experienced in the administration of intravenous bisphosphonates. In the Panel's view these physicians would be well aware that such medicines had to be used with care in patients with renal impairment and that renal function should be monitored during therapy. The Zometa SPC stated that the adverse reactions to the medicine were similar to those reported for other bisphosphonates and could be expected to occur in approximately one third of patients. The Panel did not consider that the omission of data regarding the renal toxicity of Zometa gave a misleading impression of the safety of the product. There was no implication that renal toxicity was not a problem with Zometa. The Panel thus considered that the claim 'Zometa is well tolerated' was not misleading. No breach of the Code was ruled. The Panel consequently also ruled no breach of Clause 2 of the Code. These rulings were appealed.

Upon appeal by Roche the Appeal Board noted statements in the Zometa SPC with regard to who could use the product and the incidence of adverse events compared with other bisphosphonates. The Appeal Board noted that there were some concerns regarding the renal tolerability profile of Zometa but considered that these had been exaggerated by Roche. The Appeal Board did not consider that the failure to refer to the renal tolerability profile of the product rendered the claim 'Zometa is well tolerated' misleading and unbalanced as alleged. The Panel's rulings of no breach of the Code were upheld.

Roche noted the claim 'Zometa has a fast and convenient administration', referenced to the SPC, and stated that the same issues arose here as above regarding the claim 'Zometa is quick and convenient to deliver'.

The Panel noted its comments and rulings above with regard to 'quick' and 'convenient' and considered that they applied here. The Panel thus ruled no breach of the Code with regard to fast and a breach of the Code with regard to convenient. The ruling of a breach of the Code was overturned on appeal by Novartis for the reasons given above.

Roche Products Limited complained about a Zometa (zoledronic acid) detail aid (ref ZOM03001303) issued by Novartis Pharmaceuticals UK Ltd. Zometa was presented as a concentrate for solution for infusion and licensed for the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone. It could also be used to treat tumour-induced hypercalcaemia. Roche marketed Bondronat which was available as film coated tablets and as a concentrate for solution for intravenous administration. Both formulations were indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. In addition, Bondronat IV was also indicated for the treatment of tumour-induced hypercalcaemia with or without metastases. Both Zometa and Bondronat belonged to a class of medicines known as bisphosphonates.

1 Claim 'Licensed for bone metastases in more tumour types than any other bisphosphonate'

This claim appeared as the headline on the front cover (page 1) of the detail aid.

COMPLAINT

Roche stated that the claim was vague and did not specify for what the product was being used, ie the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone. Zometa was not licensed to prevent or clear bone metastases as this claim suggested. Roche alleged that the claim was misleading in breach of Clause 7.2 of the Code.

RESPONSE

Novartis disagreed that the claim was vague. Zometa was licensed for 'Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone'. The company considered that as 'advanced malignancies involving bone' was synonymous with 'bone metastases' and 'skeletal related events' were the consequence of bone metastases the meaning of the claim was clear. There was no implication that Zometa could either prevent the occurrence of bone metastases, or clear them; given that the target audience was oncology/ haematology specialists it was unimaginable that they would infer this. Novartis did not consider that the claim was misleading and thus denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that Zometa was licensed to prevent skeletal related events in patients with advanced malignancies involving bone. The Panel considered that the claim 'Licensed for bone metastases in more tumour types than any other bisphosphonate' was not sufficiently clear in this regard; there was an implication that the product could be used to treat the metastases *per se* and that was not so. The Panel considered that the claim was misleading. A breach of Clause 7.2 was ruled.

APPEAL BY NOVARTIS

Novartis referred to the licensed indications for Zometa. Bone was one of the most common locations to which cancer metastasised. The major cancer types which tended to metastasise to bone included multiple myeloma, breast, prostate, lung, kidney and thyroid cancers. All of these were covered by the Zometa license, unlike the other bisphosphonates currently on the market which were all restricted to breast cancer +/- multiple myeloma.

Bone metastases damaged bone making it more susceptible to complications such as: pathological fractures due to intrinsic weakening of the bone caused by the metastasis; spinal cord compression leading to paralysis due to pressure on the cord from a growing metastasis, or collapse of a vertebra; hypercalcaemia due to release of bone calcium from over-activity in the skeleton caused by the growth of the metastasis. These sequelae of bone metastases were defined as 'skeletal related events'. By definition, it was not possible to have a skeletal related event without at least one bone metastasis. Researchers concluded that once these metastases appeared, sequelae would ensue which complicated the course of the disease and adversely affected quality of life.

The goals of treatment of bone metastases were to reduce morbidity and so improve quality of life. Such treatment might involve chemotherapy, hormonal therapy, radiotherapy, surgery to stabilise a weakened bone, for instance in the spine, and bisphosphonates.

Novartis noted that the term 'treatment of bone metastases' with reference to bisphosphonates was in common use in the clinical community, as it was equally applied to the use of radiotherapy in this setting. The company noted that in Rosen *et al* (2003) and Rosen *et al* (2004), the term 'treatment' was used to describe the use of zoledronic acid, or pamidronate, in patients with bone metastases. Novartis provided further examples of the use of this terminology in the medical literature (Lacerna and Hohneker 2003 and Maxwell *et al* 2003). Therefore in common parlance in the clinical community, the term 'treatment' in this context was not only well understood, but appeared to be the preferred term.

Thus, Zometa was used to treat bone metastases in order to prevent these complications, hence the wording of the licence 'Prevention of skeletal related events' in patients who already had one or more bone metastases: 'Advanced malignancies involving bone' meant the presence of bone metastases.

Novartis disagreed with the Panel's statement that 'there was an implication that the product could be used to treat the metastases *per se* and this was not so'. On the contrary, the product was used precisely to treat bone metastases as demonstrated above.

Novartis noted that Roche had alleged that the claim suggested that Zometa was licensed to prevent or clear bone metastases (which was quite distinct from treating them). However, there was no indication of this. 'Licensed for bone metastases …' implied that the condition was already present, as in 'licensed for hypertension'. It did not imply that the licence was for prevention. It also did not state that treatment would 'clear' or cure bone metastases, again analogous to 'licensed for hypertension' which did not claim a cure, merely a treatment.

Novartis did not consider that the claim was misleading or in breach of Clause 7.2.

COMMENTS FROM ROCHE

Roche stated that 'common parlance' in medicine was not a substitute for unambiguous and definite statements, as set out in the marketing authorization. The Panel was correct in its ruling of this major first claim at its face value – it implied that Zometa could be used to treat metastatic bone cancer *per se*, for which it was not licensed.

APPEAL BOARD RULING

The Appeal Board noted that the Panel had stated that Zometa could not be used to treat the metastases *per se*. The Appeal Board disagreed with this; Zometa would have an effect on bone metastases and the product was licensed to prevent five specific skeletal related events in patients with advanced malignancies involving bone. The Appeal Board considered, however, that the claim 'Licensed for bone metastases in more tumour types than any other bisphosphonate' was not sufficiently clear in this regard; there was an implication that the product could be used to prevent or clear the metastases, and that was not so. The Appeal Board considered that the claim was

ambiguous and misleading. The Panel's ruling of a breach of Clause 7.2 was upheld. The appeal on this point was unsuccessful.

2 Claim 'Broad protection from the threat of skeletal complications'

This claim appeared as a strapline below the product logo on the front cover of the detail aid and also on pages 3, 8, 9, 12 and 14.

COMPLAINT

Roche alleged that the claim was all-embracing in breach of Clause 7.10.

RESPONSE

Novartis stated that the claim clearly appeared in the context of the licence for bone metastases and was consistent with the summary of product characteristics (SPC) wording 'Prevention of skeletal related events'. The marketing authorization was supported by several large randomized trials in a wide array of solid tumour types and multiple myeloma. Novartis did not consider that the claim was all-embracing and thus denied a breach of Clause 7.10.

PANEL RULING

The Panel noted that the claim 'Broad protection from the threat of skeletal complications' appeared as a strapline beneath the Zometa product logo on the front cover of the detail aid. That, together with the claim at issue in point 1 above, was all the promotional copy that appeared on page 1. The Panel noted its comments and ruling in point 1 and considered that, given the context in which it appeared, the claim now at issue was exaggerated and all-embracing; it reinforced the impression that Zometa could be used to treat the metastases *per se* or otherwise protected patients from developing bone metastases which was not so. A breach of Clause 7.10 was ruled. This was appealed by Novartis.

The product logo and strapline also appeared at the bottom of pages 3, 8, 9, 12 and 14. Page 3 was part of a double-page spread headed 'Zometa – meeting the challenges of treating metastic bone disease' and included details of the most common skeletal related events in patients with metastatic bone disease. Pages 8 and 9 together were headed 'Zometa – a new standard for the treatment of hypercalcaemic cancer patients', page 12 dealt with the tolerability of Zometa and the prescribing information and references were given on page 14. The Panel considered that given the content of these pages the claim 'Broad protection from the threat of skeletal complications' was not unreasonable; there was no implication that Zometa prevented the patient developing metastases. The Panel noted from the licensed indication for Zometa that it could be used to prevent a number of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia). The Panel considered that, other than on page 1 of the detail aid, given the context in which it appeared the claim was not exaggerated or all-embracing. No breach of Clause 7.10 was ruled.

APPEAL BY NOVARTIS

Novartis stated that as described in point 1 above, Zometa was used for the treatment of patients with bone metastases, the claim 'Broad protection from the threat of skeletal complications' further clarified the purpose of treatment, which was to protect against skeletal complications in this disease. In addition, as it was not possible to have a skeletal complication without underlying bone metastases, this claim could not imply that Zometa protected against developing bone metastases.

Novartis did not consider that the claim was exaggerated or all-embracing or in breach of Clause 7.10.

COMMENTS FROM ROCHE

Roche stated that the claim implied that Zometa had a broad range of protection against all skeletal complications. Sustained quality of life maintenance and bone pain control had not been demonstrated over 2 years. Patients might still sustain fractures; the SPC showed a non-significant difference compared to placebo for the proportion of patients with fractures with prostate (p=0.052), breast and myeloma (p=0.653), or other solid tumours (p=0.064). Radiation therapy might not be avoided; the SPC showed non-significant differences compared to placebo for the proportion of patients with radiation to bone with prostate (p=0.119), and solid tumours other than breast and prostate (p=0.173). The claim remained a breach of Clause 7.10.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'Broad protection from the threat of skeletal complications' appeared as a strapline beneath the Zometa product logo on the front cover of the detail aid. That, together with the claim at issue in point 1 above, was all the promotional copy that appeared on page 1. The Appeal Board noted its comments and ruling in point 1 and considered that, given the context in which it appeared, the claim now at issue was exaggerated and all-embracing. The Appeal Board considered that the claim gave the impression that Zometa could provide protection from the formation of new metastases which was not so. Skeletal related events as referred to in the SPC was not the same as skeletal complications. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.10 of the Code in relation to the claim as it appeared on page 1. The appeal on this point was unsuccessful.

3 Bar chart adapted from Green *et al* (1994)

A bar chart on page 3 of the detail aid depicted the potency of seven bisphosphonates relative to pamidronate disodium *in vivo* (hypercalcaemic rat) on a linear scale. Six of the seven medicines shown had a

relative potency of less than 44. Of those six ibandronate (Bondronat) had the highest relative potency of 43.6. The relative potency of Zometa was given as 847.

COMPLAINT

Roche alleged that the bar chart misled, misrepresented and exaggerated the difference in potencies between Bondronat and Zometa in breach of Clause 7.2, 7.3 and 7.10. It was not possible to see how the bar chart had been generated from the cited reference and if it was not capable of substantiation it would breach Clause 7.5. In addition, in September 2003 (the date on which the detail aid was produced), Bondronat did not have a product licence for metastatic bone disease and, hence the chart, at that time, promoted a medicine prior to the grant of its marketing authorization. A breach of Clause 3.1 was alleged.

Roche stated that the footnote on the table of data below the chart (see point 4 below) stating that 'potency is not necessarily related to clinical efficacy', could not be used to ameliorate the impact of the clinical promotional message that was repeated at the bottom of page 3 in bold red lettering – 'Broad protection from the threat of skeletal complications'.

Roche noted the prominent use of the bar chart on the second page of a double-page spread entitled, in bold red lettering, 'Zometa – meeting the challenges of treating metastatic bone disease' and with a bold red strapline – 'Broad protection from the threat of skeletal complications'. It misled the customer into unfairly assuming greater efficacy for Zometa than Bondronat when no such data existed in breach of Clauses 7.2 and 8.1.

RESPONSE

Novartis submitted that the y axis on the bar chart was clearly labelled 'Potency relative to pamidronate disodium *in vivo* (hypercalcaemic rat), linear scale'. Green *et al* only contained one hypercalcaemic rat model (the other model was mouse calvaria and was *in vitro*), and only one table of relative potencies in this model. Relative potencies were derived from the ED50 (µg/kg SC) figures taking pamidronate as the standard. Thus, the ED_{50} for clodronate was 1,200 compared to pamidronate of 61, giving a relative potency of 0.05 (61/1,200) and so on. This was further highlighted by the authors in the 'Results' section where they stated '[Zometa], with an ED_{50} of 0.072 µg/kg SC, was the most potent of all the bisphosphonates tested to date in our laboratory' and 'Thus, [Zometa] was 850 times more potent than pamidronate …'.

Novartis submitted that the bar chart did not mislead, misrepresent or exaggerate the difference in potencies as it was clear that the figures were not a general comparison but were all derived from a single *in vivo* study as stated in the heading 'Zometa is the most potent bisphosphonate in this *in vivo* study'. Novartis denied breaches of Clauses 7.2, 7.3 or 7.10; the bar chart could be substantiated from the reference given and was not in breach of Clause 7.5.

Novartis added that the use of an *in vivo* hypercalcaemic rat model to demonstrate relative potencies could not be considered to promote Bondronat prior to its marketing authorization for metastatic bone disease, especially since, at this time point, Bondronat already had a marketing authorization for tumour-induced hypercalcaemia. Thus the bar chart could not be in breach of Clause 3.1.

Novartis stated that the general heading on page 3, 'Zometa is a highly potent bisphosphonate', was a statement of fact and not a comparison. There was also a footnote about potency and efficacy which related to the potency figures given. The strapline 'Broad protection from the threat of skeletal complications' was repeated from page 1 and referred only to the licensed indication for Zometa and did not infer comparison to other bisphosphonates. In addition, the heading on pages 2 and 3 'Zometa – meeting the challenges of treating metastatic bone disease' also referred only to Zometa and did not make any comparison to other bisphosphonates. It did not therefore mislead the customer into assuming greater efficacy for Zometa over Bondronat and was not in breach of Clause 7.2, nor did it disparage Bondronat and so it was thus not in breach of Clause 8.1.

PANEL RULING

Page 3 was part of a double-page spread headed 'Zometa – meeting the challenges of treating metastatic bone disease'; the Panel thus considered that the information given on page three would be viewed in terms of the clinical situation. Although the bar chart at issue showed that in terms of *in vivo* potency Zometa was many times more potent than the other bisphosphonates, given the context in which it appeared, some readers would assume that such relative potency translated into similar relative efficacy and that Zometa was the most efficacious bisphosphonate. The Panel further noted that although the page heading referred to metastatic bone disease the bar chart related to the treatment of hypercalcaemia. Overall the Panel considered that the bar chart was misleading and exaggerated the differences between Zometa and Bondronat as alleged. Breaches of Clauses 7.2, 7.3 and 7.10 were ruled.

The Panel noted Novartis' explanation as to how the data had been generated for the bar chart. The Panel considered that the bar chart *per se* could be substantiated. The Panel noted, however, that Roche had alleged a breach of Clause 7.5 which required substantiation for any claim etc to be provided without delay at the request of members of the health professions or appropriate administrative staff. There was no indication that data to substantiate the claim at issue had been requested or that such a request had not been complied with. No breach of Clause 7.5 was ruled.

The Panel noted that Clause 1.2 of the Code defined 'promotion' as any activity undertaken by a pharmaceutical company, or with its authority which promoted the prescription, supply, sale or

administration of *its* medicines (emphasis added). It was thus an established principle under the Code that one company could not be accused of promoting another company's products. The Panel noted that nonetheless references to competitor products had to comply, *inter alia*, with Clause 7.2. There was however, no allegation in this regard. The Panel considered, therefore, that although the bar chart referred to Roche's product ibandronate, regardless of what it was licensed for Novartis could not be accused of promoting it. No breach of Clause 3.1 was ruled.

The Panel considered that the bar chart was misleading with regard to the implied relative efficacy of Bondronat and Zometa but considered that this was covered by its ruling of a breach of Clause 7.2 above. The Panel did not, however, consider that the bar chart disparaged Bondronat. No breach of Clause 8.1 was ruled.

APPEAL BY NOVARTIS

Novartis noted that the bar chart appeared under a banner heading 'Zometa – meeting the challenges of treating metastatic bone disease'. The clear and unambiguous heading 'Zometa is the most potent bisphosphonate in this *in vivo* study', referred very specifically to Green *et al* and gave no opportunity to mislead that the evidence presented was in a clinical setting. The chart also had an over-arching statement 'Zometa is a highly potent bisphosphonate'. This was a matter of fact. The chart then explained the pre-clinical basis for the claim. The fact that the pre-clinical rat model was in hypercalcaemia (not bone metastases) was not relevant as it was a model for potency alone, not for clinical efficacy.

Novartis stated that the detail aid was aimed at oncologists and haematologists, a specialist rather than generalist audience. These doctors generally worked in tertiary referral centres, and many were academics. Clinicians of this calibre found scientific data – including pre-clinical data – useful as it added to the overall information on a product allowing them to make an informed decision.

Novartis disagreed that the chart misled the reader, given the very clear heading, and therefore did not consider it to be in breach of Clause 7.2. Novartis considered that, in the context of the clearly labelled *in vivo* study, the comparison of products – in this narrow definition was acceptable and therefore not in breach of Clause 7.3. Equally, in this narrow definition, the difference between Zometa and ibandronate was not exaggerated, but an accurate reflection of the study, and therefore not in breach of Clause 7.10.

COMMENTS FROM ROCHE

Roche stated that putting this misleading chart (adapted by Novartis to exaggerate the potency of Zometa) amidst a discussion of clinical efficacy was clearly designed to imply clinical relevance. Roche submitted that the chart could not be read in isolation on the page. Roche concurred with the Panel's ruling.

APPEAL BOARD RULING

The Appeal Board noted that page 3 was part of a double-page spread headed 'Zometa – meeting the challenges of treating metastatic bone disease' and thus considered that the information on both pages would be viewed in terms of the clinical situation. Although the bar chart at issue showed that the *in vivo* potency of Zometa was many times greater than the other bisphosphonates, given the context in which it appeared, some readers would assume that such relative potency translated into similar relative efficacy and the bar chart showed that Zometa was the most clinically efficacious bisphosphonate. Overall the Appeal Board considered that the bar chart was misleading and exaggerated the differences between Zometa and Bondronat as alleged. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.10 of the Code. The appeal on this point was unsuccessful.

4 Table of data on page 3

A table of data below the bar chart at issue in point 3 above compared the relative potency (*in vivo*), infusion time, bioavailability and route of administration of Zometa, pamidronate and oral clodronate. It was noted that with oral preparations, patients had to adhere to a strict dosing schedule and that the potential for poor compliance and treatment failure was high.

COMPLAINT

Roche complained that Bondronat had not been included in the table. Bondronat had been commercially available for metastatic bone disease since March 2004. To not include reference to the product in the detail aid was unbalanced in breach of Clause 7.2 of the Code.

Roche further noted that although comments were made about the posology of other bisphosphonates, no caution was discussed about Zometa and its use related to renal function ie it could not be used in a patient with a creatinine clearance < 30ml/min and there were concerns over concomitant use with other potentially nephrotoxic agents. This was unbalanced in breach of Clause 7.2.

RESPONSE

Novartis stated that the detail aid had been withdrawn in January 2004 to coincide with the launch of a new formulation of Zometa (from the old freeze dried powder to the new solution for infusion). The detail aid was thus withdrawn prior to the marketing authorization for Bondronat in metastatic bone disease in breast cancer, therefore failure to mention the product in the clinical context of treating metastatic bone disease was hardly unreasonable at that time and could not be considered unbalanced or in breach of Clause 7.2.

Novartis disagreed with Roche's comments in relation to the posology of other bisphosphonates in this table. The table had a bold heading about bioavailability and the table clearly related to this. There was a

single comment at the bottom of the table about compliance with oral agents which had direct relevance to the issue of bioavailability and the timings (from the SPC) required for oral clodronate to be taken were given and again were directly relevant to its bioavailability. Novartis failed to see the relevance of Roche's comments about the use of Zometa in patients with severely impaired renal function in the context of a table about bioavailability, particularly when Roche had not indicated that similar cautions for the other agents discussed should be mentioned. Novartis therefore disagreed that, in the context of bioavailability, the table was unbalanced and thus denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the leavepiece pre-dated Bondronat's licence for use in metastatic bone disease. The Panel thus ruled no breach of Clause 7.2 of the Code with regard to the omission of Bondronat from the table of data at issue.

The Panel noted that the table of data detailed relative potency (*in vivo*), infusion time (minutes), availability % and route of administration. None of these headings related to the use of the bisphosphonates listed in patients with impaired renal function. The Panel therefore did not consider that omission of such data with regard to Zometa from the table in question was misleading. No breach of Clause 7.2 was ruled.

5 Claim 'Statistically significant effects were achieved at low concentration'

This claim appeared at the bottom of page 4 beneath a statement that pre-clinical studies had shown significant effects of Zometa on cancer cells and its ability to interfere with the metastatic process in bone in animal models.

COMPLAINT

Roche alleged that the claim, offered without further explanation or references, was all-embracing in breach of Clause 7.10 and possibly Clause 7.5. Such effects were commonly seen with bisphosphonates and the page imputed special merit from pre-clinical data where there might be none.

RESPONSE

Novartis noted that the claim was the last point on a page entitled 'Zometa – a potent inhibitor of osteolytic bone resorption and osteosclerotic bone formation' which was referenced and described how Zometa worked. It was not a stand-alone statement and could not be considered to be all-embracing in this context. It was not in breach of Clause 7.10, and since it was clearly referenced, nor was in breach of Clause 7.5.

Novartis did not entirely understand Roche's point about these effects being seen commonly with bisphosphonates and this implying some special merit from pre-clinical data. The mechanism of action shown was consistent with the references cited, and also with Section 5.1 of the Zometa SPC and therefore it was not an exaggerated claim or in breach of Clause 7.10.

PANEL RULING

Page 4 detailed Zometa's mode of action and featured a diagram showing that it mediated osteosclerotic bone formation and inhibited osteolytic bone resorption. The Panel did not consider, given the context in which it appeared, that the claim at issue, 'Statistically significant effects were achieved at low concentration' was exaggerated, all-embracing or that it implied special merit from pre-clinical data where there might be none. No breach of Clause 7.10 was ruled.

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

6 Claim 'Zometa – superior to pamidronate in reducing the risk of bone complications in advanced breast cancer'

This claim appeared as the headline to page 5 and was referenced to data on file.

COMPLAINT

Roche stated that the claim implied that all patients with advanced breast cancer would benefit. This was an all-embracing claim in breach of Clause 7.10 and was not true in breach of Clause 7.2. These data referred to patients who were undergoing hormonal therapy and who had suffered from hypercalcaemia of malignancy – hence, a highly selected subset. The 'data on file' used to support this claim consisted of four tables from a confidential report. This data had been supplied on request with a few hand scribbled calculations but without explanation. Roche considered that this failed to adequately substantiate the claim in breach Clause 7.4.

Roche added that apart from radiation to bone (a secondary endpoint), the original publication showed that the primary endpoint of non-inferiority was reached, ie Zometa was no worse than pamidronate (Rosen *et al* 2001). The SPC also stated 'Zometa 4mg showed comparable efficacy to 90mg pamidronate in the prevention of [Skeletal Related Events]'. Although the SPC included a statement of benefit over pamidronate, this was based on a secondary endpoint of the trial. The claim that Zometa was superior to pamidronate was therefore not consistent with the SPC in breach of Clause 3.2.

RESPONSE

Novartis disagreed with Roche's interpretation of what it considered to be a fairly straightforward claim based on the results cited in Section 5.1 of the Zometa SPC as follows: 'In a third phase III randomised,

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

Novartis submitted that this showed superiority (a 16% risk reduction) of Zometa over pamidronate for the entire patient population including both multiple myeloma and breast cancer patients. Roche's statement that these data only referred to breast cancer patients who were undergoing hormonal therapy and who had suffered from hypercalcaemia of malignancy was wrong. Not only was Zometa superior to pamidronate in the study population as a whole, taking the group of patients with breast cancer (including those with and without hypercalcaemia and those treated with either chemotherapy or hormonal therapy) the risk reduction on Zometa was 20% compared to pamidronate, and 30% in the subset of patients with breast cancer who received hormonal therapy. Therefore the claim was not in breach of either Clause 7.10 or Clause 7.2.

The data on file supporting this claim was supplied to Roche on request and adequately supported the claim if the figures given in the tables supplied were analysed (the hand written calculations showed how the analysis was derived). Therefore the claim could be substantiated and was not in breach of Clause 7.4. The data on file related to the 25 month follow-up data which had subsequently been published (Rosen *et al*, 2003 and Rosen *et al* 2004). These papers both concluded that 'Zoledronic acid 4mg is more effective than pamidronate 90mg in reducing the risk of developing skeletal complications in the overall population and in patients with breast carcinoma' and '[Zoledronic acid] appeared to be more effective than pamidronate in patients with breast carcinoma and at least one osteolytic lesion'. Novartis stated that since these data had now been published, it no longer used the data on file as a reference document.

Novartis submitted that the statement was consistent with Section 5.1 of the Zometa SPC and was therefore not in breach of Clause 3.2.

PANEL RULING

The Panel noted that the claim at issue 'Zometa – superior to pamidronate in reducing the risk of bone complications in advanced breast cancer' was referenced to data on file. That data had now been published as Rosen *et al* (2003) and Rosen *et al* (2004). These data did not, as submitted by Roche, refer only to those who were undergoing hormonal therapy.

Rosen *et al* (2003) looked at the treatment of skeletal complications in patients with advanced multiple myeloma or breast cancer. Rosen *et al* (2004) looked at the treatment of bone metastases in breast cancer patients with at least one osteolytic lesion. Rosen *et al* (2003) stated that in patients with breast cancer Zometa 4mg was significantly more effective than pamidronate, reducing the risk of skeletal related events by an additional 20% (p=0.025) compared with pamidronate and by an additional 30% in patients receiving hormonal therapy (p=0.009).

Rosen *et al* (2004) stated that multiple-event analysis showed a 20% additional reduction in the risk of skeletal events (p=0.037) for Zometa-treated patients compared with those taking pamidronate. In patients with lytic lesions although the primary endpoint (the proportion of patients with a skeletal event) did not achieve statistical significance, multiple-event analysis demonstrated that the benefit of Zometa was even greater compared with pamidronate with an additional 30% reduction in the risk of skeletal events, a secondary endpoint, being observed (p=0.01). The Panel noted that the discussion section of Rosen *et al* (2004) stated that the data strongly suggested that Zometa might be more effective clinically compared with pamidronate in patients with breast cancer and at least one osteolytic lesion and in the overall population of patients with breast carcinoma. Such caution was not reflected in the claim at issue. The Panel considered that the headline claim was not a fair reflection of the study results and was misleading and exaggerated in that regard. Breaches of Clauses 7.2 and 7.10 were ruled.

The Panel noted that at the time the claim was made the two papers by Rosen *et al* had not been published; all that was available was the data on file which consisted of 4 pages of tables showing hazard ratios, p values and robust p values for the various treatments. Some handwritten calculations were included on two of the tables. The Panel noted that the breast cancer data were given according to whether patients received chemotherapy or hormonal therapy. The Panel considered that the presentation of the data on file was such that it was difficult to understand and was inadequate to substantiate the claim at issue. A breach of Clause 7.4 was ruled.

The Panel noted that the Zometa SPC stated that in a combined patient group of those with multiple myeloma or breast cancer with at least one bone lesion, Zometa and pamidronate had comparable efficacy in prevention of skeletal related events. The claim at issue related only to patients with breast cancer. In that regard the Panel did not consider that the claim was inconsistent with the particulars listed in the SPC. No breach of Clause 3.2 was ruled.

APPEAL BY NOVARTIS

Novartis stated that bone metastases were present in 60 – 80% of patients with metastatic (advanced) breast cancer ie the most common site of tumour metastases in these patients. In addition, to reduce the risk of *bone complications* (specifically, not to reduce the risk of developing bone metastases), it was implicit that bone metastases were present (and, of course, in the majority of advanced disease, they were).

The claim was based on a study of 1,648 patients with at least one bone lesion secondary to multiple myeloma or advanced breast cancer. The primary endpoint was to demonstrate non-inferiority of Zometa to pamidronate, an active control, in the proportion of patients experiencing at least one skeletal related event (pathological fracture, spinal

cord compression, radiation to bone and surgery to bone, ie complications of bone metastases). That endpoint was achieved at the initial 13 month analysis and the final 25 month analysis (Rosen *et al* 2003).

As stated in Rosen *et al* (2003) 'For the primary efficacy analysis, HCM [hypercalcaemia of malignancy] was not included in the definition of SREs [skeletal related events], because zoledronic acid has already demonstrated efficacy in treating HCM. However, HCM is a clinically important event that can be life threatening; therefore, some secondary efficacy analyses included HCM, defined as a serum calcium ≥ 12mg/dL. Secondary efficacy endpoints included the proportion of patients experiencing an SRE, the proportion of patients experiencing each type of SRE, time to first SRE, time to each type of SRE, skeletal morbidity rate, multiple-event analysis, overall survival, and ECOG [Eastern Cooperative Oncology Group] performance status changes'.

Novartis stated that these secondary endpoints were both clinically relevant and important, whereas the primary endpoint was a statistical one to demonstrate non-inferiority. Rosen *et al* (2003) further stated that a 'pre-planned multiple-event analysis was performed using the Andersen-Gill approach, and the robust estimate of variance was used to calculate P values'. This multiple event analysis was the most sensitive and statistically robust measure of skeletal morbidity and also clinically very useful as it '…captures data on all clinically relevant SREs and the time to each event, thus providing a comprehensive assessment of skeletal morbidity' (Rosen *et al* 2004).

Novartis noted that Rosen *et al* (2003) stated, with regard to the multiple event analysis 'Treatment with 4mg zoledronic acid reduced the risk of developing a skeletal complication by an additional 16% compared with pamidronate in the overall patient population'. This fact was reflected in Section 5.1 of the Zometa SPC. Turning to the subset analysis in patients with breast carcinoma ie excluding those with multiple myeloma, the multiple event analysis showed that 'among all breast cancer patients, 4mg zoledronic acid significantly reduced the risk of developing any skeletal complications (including HCM) by an additional 20% compared with pamidronate (risk ratio, 0.799; 95% CI, 0.657 – 0.972; $P = 0.025$)'. This data was demonstrated graphically beneath the claim 'Zometa – superior to pamidronate in reducing the risk of bone complications in advanced breast cancer'.

Rosen *et al* (2004) described a retrospective subset analysis ie unplanned, unlike the multiple event analysis described above, of the breast cancer patients from the same study separated by radiologic appearance of their bone lesions (lytic, blastic or mixed). This post hoc analysis determined that in the group of patients with lytic lesions, Zometa reduced the risk of a skeletal complication by an additional 30% compared with pamidronate. Unfortunately, the Panel had concentrated on Rosen *et al* (2004), the post hoc analysis, rather than Rosen *et al* (2003) which reported the pre-planned analyses that clearly demonstrated that Zometa was superior to pamidronate in the study population as a whole, and in particular in all patients with breast cancer included in the trial on the clinically relevant multiple event analysis.

Novartis did not consider that the claim was an unfair reflection of the study results nor misleading and therefore it was not in breach of Clauses 7.2 or 7.10.

COMMENTS FROM ROCHE

Roche noted that Novartis stated that 'secondary endpoints were both clinically relevant and important'. According to the SPC, superiority was not demonstrated for patients with breast cancer or myeloma in the following analyses: proportion of patients with SREs (p=0.198); proportion of patients with fractures (p=0.653); median time to SRE (p=0.151); median time to fracture (p=0.672); skeletal morbidity rate for SREs (p=0.084) and skeletal morbidity rate for fractures (p=0.614).

Roche stated that the Panel had taken a balanced view of the two Rosen papers. Multiple event analysis was criticised by the Council of the American Society of Clinical Oncology as a statistical tool in its latest guidelines: 'Analysis based on multiple event data must be interpreted with care … and require making somewhat arbitrary decisions about how to represent events …' They 'may be subject to after the fact assumptions, and ideally, should be independently validated. The panel concluded there was insufficient evidence to conclude that the effectiveness of zoledronic acid was superior to pamidronate.'

Roche alleged that the claim misled and exaggerated the SPC position as set out in table 4 of the SPC.

APPEAL BOARD RULING

The Appeal Board noted that the claim at issue 'Zometa – superior to pamidronate in reducing the risk of bone complications in advanced breast cancer' was referenced to data on file which had now been published as Rosen *et al* (2003) and Rosen *et al* (2004). Rosen *et al* (2003) described a pre-planned, prospective analysis of the data and stated that in patients with breast cancer Zometa 4mg was significantly more effective than pamidronate, reducing the risk of skeletal related events by an additional 20% (p=0.025) compared with pamidronate and by an additional 30% in patients receiving hormonal therapy (p=0.009). Rosen *et al* (2004), which was a *post-hoc* retrospective analysis of the data, stated that multiple-event analysis showed a 20% additional reduction in the risk of skeletal events (p=0.037) for Zometa-treated patients compared with those taking pamidronate. In patients with lytic lesions although the primary endpoint (the proportion of patients with a skeletal event) did not achieve statistical significance, multiple-event analysis demonstrated that the benefit of Zometa was even greater compared with pamidronate with an additional 30% reduction in the risk of skeletal events, a secondary endpoint, being observed (p=0.01). The Appeal Board considered that the headline claim was a fair reflection of the data and as such was not misleading or exaggerated. No breaches of Clauses 7.2 and 7.10 were ruled. The appeal on this point was successful.

7 Claim 'Zometa – effective bone protection in breast cancer'

This claim appeared on page 5 below a chart which showed that breast cancer patients treated with Zometa had a 20% lower risk of developing skeletal complications compared with pamidronate. The claim was referenced to data on file.

COMPLAINT

Roche alleged that the claim was inconsistent with the licensed indication 'Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with *advanced* malignancies involving bone' (emphasis added). Zometa was not licensed for breast cancer *per se*, nor adjuvant use to prevent bone metastases, as this claim promoted. Roche alleged a breach of Clause 3.1. In addition, this claim was supported by data on file from a confidential report. Again, it was supplied on request with a few hand scribbled calculations but without explanation. These data did not readily demonstrate statistically how this claim was generated, as there was no mention of bone pain scores. Roche considered that the data did not substantiate the claim in breach of Clause 7.4.

RESPONSE

Novartis noted that the claim appeared on a page which was headlined 'Zometa – superior to pamidronate in reducing the risk of bone complications in advanced breast cancer' and above the statement 'Zometa consistently reduces the incidence of all types of skeletal-related events (SREs)' and was therefore clearly in the context of breast cancer with bone metastases. Zometa was not licensed for breast cancer *per se*, nor for adjuvant use to prevent bone metastases and in context this claim did not promote these indications and was not in breach of Clause 3.1.

Novartis noted that, as in point 6 above, the data on file was supplied to Roche on request and gave the tables of figures from which the claim was derived. Therefore it was not in breach of Clause 7.4. As above, since these data had now been published, Novartis no longer used the data on file as a reference document.

PANEL RULING

The Panel noted that the claim 'Zometa – effective bone protection in breast cancer' appeared on a page on which the heading referred to 'advanced breast cancer'. The page tag, however, stated 'Zometa – in breast cancer'. In that context the Panel considered that the claim at issue implied that Zometa was authorized for use in all breast cancer patients which was not so. The claim was inconsistent with the particulars listed in the SPC. The Panel ruled a breach of Clause 3.1 as alleged.

The Panel noted its comments in point 6 above with regard to the data on file and considered that its ruling of a breach of Clause 7.4 also applied here.

APPEAL BY NOVARTIS

Novartis noted that the claim appeared below the heading 'Zometa – superior to pamidronate in reducing the risk of bone complications in advanced breast cancer' and the sub-heading 'Multiple event analysis showed patients treated with Zometa had a **20% lower risk** of developing skeletal complications compared to pamidronate ($p = 0.025$). Both the heading and sub-heading were in very large type. In context, the claim seemed reasonable. It could not be read in isolation on the page, which included statements about advanced breast cancer and skeletal complications. Moreover, the entire detail aid was about skeletal complications.

Novartis noted that the Panel implied that the page tag 'Zometa – in breast cancer', which was in considerably smaller font than the heading or sub-heading (and rotated through 90°), negated the context of the entire page. However, on opening the page (having seen the front of the detail aid which was about bone metastases), and starting to read from the top it was immediately apparent that the context was advanced breast cancer.

Novartis disagreed that the claim, in the context in which it appeared, was inconsistent with the SPC and thus denied a breach of Clause 3.1.

COMMENTS FROM ROCHE

Roche stated that this large, bold claim (on a page tabbed 'Zometa – in breast cancer') implied adjuvant use, for which Zometa was not licensed. Roche concurred with the Panel.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'Zometa – effective bone protection in breast cancer' was unqualified with regard to the severity of breast cancer although it appeared on a page on which the heading referred to 'advanced breast cancer'. The page tag, however, was also unqualified and stated 'Zometa – in breast cancer'. Given the context in which it appeared the Appeal Board on balance considered that the claim at issue implied that Zometa was authorized for use in all breast cancer patients which was not so. The claim was thus inconsistent with the particulars listed in the SPC. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.1 of the Code. The appeal on this point was unsuccessful.

8 Claim 'Zometa consistently reduces the incidences of all types of skeletal-related events (SREs)' and associated bar chart

The claim and bar chart appeared on page 5 and were referenced to the data on file referred to at points 6 and 7 above. The bar chart showed numerical values for Zometa versus pamidronate in terms of the percentage of patients with fracture (all types), radiation to bone, surgery to bone and spinal cord compression.

COMPLAINT

Roche noted that, apart from radiation to bone (a secondary end point), the original showed that the primary end point of non-inferiority was reached, ie Zometa was no worse than pamidronate. The SPC also stated 'Zometa 4mg showed comparable efficacy to 90mg pamidronate in the prevention of SREs'. In the absence of values of significance on the bar chart, the reader could not evaluate this claim, which was misleading in breach of Clause 7.2 and all-embracing in breach of Clause 7.10.

RESPONSE

Novartis submitted that the claim was an accurate reflection of the conclusions of the study in question. It made no reference to the significance, or otherwise, of each individual end point but demonstrated graphically that, in absolute terms, in all cases (consistently) the percentage of patients with each of the skeletal related events shown was indeed reduced in the Zometa arm compared with the pamidronate arm. Therefore this claim was neither misleading nor all-embracing. Novartis denied breaches of Clauses 7.2 and 7.10.

PANEL RULING

The Panel noted that the statement in the SPC that Zometa was comparable to pamidronate in the prevention of skeletal related events referred to a study of patients with multiple myeloma or breast cancer with at least one bone lesion. The bar chart showed only the breast cancer data. The Panel noted that although the bar chart showed that, compared with pamidronate, Zometa reduced the percentage of patients with each skeletal related event, there was no information given to whether there were statistically significant differences between the two medicines. The clinical significance of the differences was not mentioned. The Panel considered that the claim and the bar chart were misleading; a breach of Clause 7.2 was ruled. The Panel also considered that the claim was all-embracing. A breach of Clause 7.10 was ruled.

APPEAL BY NOVARTIS

Novartis noted that the claim and bar chart were on the same page as considered at point 7 above. The chart showed the absolute percentages of patients experiencing various types of skeletal related events on either Zometa or pamidronate. None of the differences were statistically significant (and this was obvious in the graph), but in every case (consistently), the absolute reduction in incidence was greater in the Zometa group compared to the pamidronate group. The clinical significance again needed to be put in context of the whole page which described the overall superiority – including statistical significance in the clinically relevant multiple event analysis of Zometa to pamidronate. The claim and bar chart would not be seen in isolation.

Novartis did not consider that the claim and bar chart were misleading as it gave actual percentages, or all embracing, and therefore denied a breach of Clause 7.2 or 7.10.

COMMENTS FROM ROCHE

Roche stated that only non-significant trends existed. The company concurred with the Panel.

APPEAL BOARD RULING

The Appeal Board noted that although the claim at issue referred to all skeletal related events the incidence of tumour related hypercalcaemia was not shown on the bar chart. Although there was a numerical advantage for Zometa with regard to each skeletal related event there was no indication on the bar chart as to the statistical significance of any of the data; all of the advantages shown for Zometa could thus have been chance findings. The Appeal Board considered that the claim was misleading and all-embracing as alleged. The Panel's rulings of breaches of Clauses 7.2 and 7.10 were upheld. The appeal on this point was unsuccessful.

9 Claim 'Consistently lower pain scores reported throughout the study' and associated bar chart showing an advantage for Zometa compared with placebo over the course of two years

This claim and bar chart appeared on page 7 of the detail aid. The claim was referenced to Saad *et al* (2003) and Saad *et al* (2002).

COMPLAINT

Roche noted that the bar chart showed eight study periods over the 24 months of the study. Bone pain scores were statistically significantly different to placebo at only half of those study periods and, even then, details of the actual 'p' number were not given – just 'p<0.05'. Roche alleged that the claim was misleading in breach of Clause 7.2 and all-embracing in breach of Clause 7.10.

RESPONSE

Novartis submitted that, as in the bar chart considered in point 8 above, the use of the word 'consistently' did not imply statistical significance, but indicated that at all time points the pain scores were lower on Zometa than on placebo. The points which were statistically significant, at the accepted p value of <0.05, were indicated with an asterisk. Hence this claim was not misleading or all-embracing and not in breach of Clause 7.2 or 7.10.

PANEL RULING

The Panel noted that it had not been provided with a copy of the cited references by either party. The visual impression of the bar chart was that at every time point Zometa-treated patients had lower pain scores than those treated with placebo and that such differences were meaningful. This was not so. At months 6, 12, 15 and 18, although there was a trend to a lower pain score with Zometa, there was no

statistically significant difference between it and placebo. The Panel did not consider that use of the word 'consistently' served to negate the otherwise misleading impression. A breach of Clause 7.2 was ruled. The Panel considered that the claim was all-embracing. A breach of Clause 7.10 was ruled.

APPEAL BY NOVARTIS

Novartis noted that the bar chart showed various time points throughout a two year study and at every one of these time points, the difference in pain scores favoured Zometa, with the difference achieving statistical significance at some points, most notably, at the end of the study. Novartis noted that at the time points when statistical significance was reached, this was not marginal (at 3 months p=0.003; 9 months p=0.03; 21 months p=0.014 and 24 months p=0.024).

Novartis noted the Panel's statement 'The visual impression of the bar chart was that at every time point Zometa-treated patients had lower pain scores than those treated with placebo and that such differences were meaningful. This was not so'.

Novartis submitted that 'consistently' had no statistical meaning. Various definitions of 'consistent' were: in agreement; compatible, being in agreement with itself; coherent and uniform, reliable, steady, in mathematics as having at least one common solution, as of two or more equations or inequalities and holding true as a group; not contradictory.

Therefore it was not inappropriate to describe the pain scores throughout the study as 'consistently lower' in the Zometa group.

COMMENTS FROM ROCHE

Roche stated that Novartis had answered the issue with the given definitions of 'consistent' in its appeal. Bearing in mind only half the data points showed statistically relevant differences, the results were not 'in agreement', 'uniform', or 'holding true'.

In addition, pain scores progressively increased in this study as shown by this chart (presumably due to disease progression) – certainly, the scores were not 'consistent' between months 3 and 24.

APPEAL BOARD RULING

The Appeal Board noted that the claim was based on a long-term study which had shown a difference in pain scores for Zometa and placebo. Although only four of the eight time points were statistically significant, these were clearly marked and a p value given. By default there must have been no statistically significant differences at the other time points. The Appeal Board considered that this bar chart was different to the one at issue in point 8 above. The Appeal Board considered that the bar chart was clear and was not misleading and no breach of Clause 7.2 was ruled. The Appeal Board did not consider that the claim was all-embracing. No breach of Clause 7.10 was ruled. The appeal on this point was successful.

10 Claim 'Zometa – a new standard for the treatment of hypercalcaemic cancer patients'

This claim appeared as a headline across pages 8 and 9 of the detail aid.

COMPLAINT

Roche alleged that as Zometa was launched for the treatment of hypercalcaemia in April/May 2001, which was more than 12 months ago, the use of 'new' was in breach of Clause 7.11. Roche also alleged that the claim was all-embracing in breach of Clause 7.10 as it suggested Zometa could be used to treat any cause of hypercalcaemia in cancer. The Zometa SPC stated that the use of this medicine in this indication was limited to 'tumour-induced' hypercalcaemia. Other causes of hypercalcaemia included endocrine disorders (eg hyperparathyroidism), medicines (eg thiazide diuretics, excessive calcium supplementation), granulomatous disorders (eg tuberculosis), immobilisation and miscellaneous (eg phaeochromocytoma). These were not within the licensed indications for Zometa.

Roche stated that although it was highly likely that a patient's hypercalcaemia was due to their malignancy, it was not automatically the case. This claim was therefore all-embracing in breach of Clause 7.10, and outside of the marketing authorization in breach of Clause 3.1.

RESPONSE

Novartis denied a breach of Clause 7.11 because 'new' clearly referred to the standard and not to the product or presentation.

The claim was not all-embracing when viewed in a clinical setting bearing in mind that the target audience was oncologists and haematologists. Novartis submitted that the other causes of hypercalcaemia listed by Roche were exceedingly rare. If a patient with known malignancy presented with hypercalcaemia, as a matter of common clinical practice they would be treated for assumed tumour-induced hypercalcaemia in the first instance, whatever the actual cause, since this was by Roche's own admission, 'highly likely'. Therefore, this claim was not in breach of Clause 7.10 or 3.1.

PANEL RULING

The Panel noted that Clause 7.11 of the Code stated that the word 'new' must not be used to describe any product or presentation which had been generally available, or any therapeutic indication which had been generally promoted, for more than 12 months in the UK. In the claim at issue 'new' was used to describe the standard of care, not Zometa. In that regard the Panel considered that there had been no breach of Clause 7.11 and ruled accordingly.

The Panel noted both parties' submission that, in patients with cancer, hypercalcaemia was likely to be tumour-induced as opposed to due to any other cause. The page tags of pages 8 and 9 read 'Zometa-tumour induced hypercalcaemia'. The Panel thus did not consider the claim 'Zometa – a new standard for

the treatment of hypercalcaemic cancer patients' was all-embracing. No breach of Clause 7.10 was ruled. The Panel also did not consider that the claim promoted Zometa for an unlicensed indication. No breach of Clause 3.1 was ruled.

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

This claim appeared on page 10 of the detail aid. The claim was referenced to Rosen *et al* (2001). This was followed by a chart showing the relative risk of Zometa versus pamidronate in multiple myeloma. The p value was p=0.593.

COMPLAINT

Roche alleged that the claim was misleading, in breach of Clause 7.2 of the Code, as implied an advantage for Zometa whereas there was no significant difference between it and pamidronate (p=0.593).

RESPONSE

Novartis submitted that Zometa did have an advantage over pamidronate as demonstrated in the chart below the statement. The p value was given and was not significant, but there was a reduction in relative risk and therefore the statement, which made no mention of statistical significance, was not misleading or in breach of Clause 7.2.

PANEL RULING

The Panel noted that, statistically, there was no significant difference between Zometa and pamidronate; both were equally effective in decreasing the risk of skeletal complications in multiple myeloma. The fact that numerically the results favoured Zometa could have been a chance finding. The Panel thus considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

APPEAL BY NOVARTIS

Novartis noted that the claim 'Zometa decreases the risk of a skeletal complication in multiple myeloma compared to pamidronate' was based on the same trial as the breast cancer data discussed above and published by Rosen *et al*. As already discussed, 'Treatment with 4mg zoledronic acid reduced the risk of developing a skeletal complication by an additional 16% compared with pamidronate in the overall patient population'. This group included patients with multiple myeloma, although the difference between zoledronic acid and pamidronate was not statistically significant in these patients. However, p= 0.593 was printed in large, bold type on the chart accompanying this claim, and no mention was made of significance. In addition, this item was used with a specialist audience well versed in the significance, or otherwise, of given p values.

Novartis did not consider that the claim was in breach of Clause 7.2.

COMMENTS FROM ROCHE

Roche made no further comment.

APPEAL BOARD RULING

The Appeal Board noted that, statistically, there was no significant difference between Zometa and pamidronate; both were equally effective in decreasing the risk of skeletal complications in multiple myeloma. The fact that numerically the results favoured Zometa could have been a chance finding. The Appeal Board thus considered that the claim was misleading as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

12 Claim 'Zometa has superior efficacy to pamidronate disodium in hypercalcaemic cancer patients'

This claim appeared as one of five bullet points on page 11 of the detail aid which was headed 'Zometa – summary'. The claim was referenced to Major *et al* (2001).

COMPLAINT

Roche stated that the claim implied that all hypercalcaemic cancer patients would benefit. The data only referred to breast cancer patients who were undergoing hormonal therapy and who had suffered from hypercalcaemia of malignancy – a highly selected subset. Also, as noted in point 10 above, not all hypercalcaemic cancer patients would have tumour-induced hypercalcaemia. Roche alleged therefore that the claim was all-embracing in breach of Clause 7.10 and was not true in breach of Clause 7.2.

RESPONSE

Novartis noted that Major *et al* reported on the two pivotal hypercalcaemia trials. Patients taking part had the following primary cancer sites: lung, breast, multiple myeloma, head and neck, renal, unknown, haematologic and other. The Zometa SPC reflected these trial data in Section 5.1. Roche's assertion that these data only referred to breast cancer patients was therefore inaccurate.

For the same reasons given in point 10 above ie the clinical assessment of cancer patients with hypercalcaemia (which were the inclusion criteria for the studies) the claim was not all-embracing and not in breach of Clause 7.10 or Clause 7.2.

PANEL RULING

The Panel noted that Major *et al* had recruited patients ≥ 18 years of age with histological or cytological confirmation of cancer and severe hypercalcaemia of malignancy. Patients were not limited to those with breast cancer undergoing hormonal therapy as alleged; demographic details showed that patients had a wide range of primary cancer sites. With regard to the cause of hypercalcaemia, the Panel noted its comments in point 10 above that, in patients with cancer, hypercalcaemia was likely to be tumour-

induced as opposed to due to any other cause. The Panel considered that, in the context in which it appeared, ie on a page summarising all that had gone before, the claim was not misleading or all-embracing as alleged. No breach of Clauses 7.2 and 7.10 were ruled.

13 Claim 'Zometa is quick and convenient to deliver'

This claim appeared as the last of the five bullet points on page 11 of the detail aid which was headed 'Zometa – summary'. The claim was referenced to the Zometa SPC.

COMPLAINT

Roche stated that 'quick' was not a medical term; it was vague and without substantiation. 'Quick' did not appear in the SPC and so it was in breach of Clause 7.5. It also misled the reader in breach of Clause 7.2 as patients required a pre-dose renal test to comply with the SPC requirement that 'Zometa is not recommended in patients with severe renal failure' and for 'the measurement of renal function prior to each dose. In all patients with bone metastases, the dose should be withheld if renal function has deteriorated'. Roche noted that the pivotal trial was set up to show that a bolus injection could be used with Zometa which could reasonably be described as quick. However, this was toxic and had to be abandoned in favour of a 15 minute infusion. A 15 minute infusion was not 'quick' and the claim was thus misleading.

With respect to 'convenient to deliver', Roche noted that the patient must usually: attend hospital as an out patient (which necessitated transportation); have bloods taken to check for renal function; have a vein cannulated and an infusion given; have medical and nursing attendance; have the intravenous line taken down; be checked to ensure they can safely be sent home and require transportation to get home. The whole process could not be described as 'convenient' for the healthcare staff or the patient, especially where the only reason to visit hospital was to receive a bisphosphonate. Intravenous care at home also carried difficulties and risks. Roche alleged that the claim was misleading in breach of Clause 7.2.

RESPONSE

Novartis noted that 'quick' could be defined as 'capable of rapid movement or action' (Collins English dictionary). It was not an absolute term, was well understood and could hardly be considered vague. Most clinicians would accept that a 15 minute infusion was 'quick'. By comparison Novartis noted that the infusion times for other bisphosphonates range from 1 hour (Bondronat) to 4 hours (single dose clodronate). The claim at issue was consistent with the Zometa SPC and therefore capable of substantiation and not in breach of Clause 7.5. The fact that renal function monitoring was recommended before each dose of Zometa was irrelevant, as this test could be done at the patient's leisure at their local GP surgery if desired. Therefore the statement was not misleading in this respect and not in breach of Clause 7.2.

Novartis submitted that 'convenient' could be defined as 'suitable or opportune, easy to use' (Collins English dictionary). Thus insofar as any medicine, perhaps particularly those for patients with cancer, was inconvenient, the administration of Zometa could reasonably be described as 'convenient'. This claim was not misleading in that regard or in breach of Clause 7.2.

PANEL RULING

The Panel noted that, the claim at issue appeared on a page which summarized the data on Zometa and compared the product with other bisphosphonates. The claim 'Zometa is quick and convenient to administer' would be read in that context.

Compared with Bondronat or Aredia, Zometa could be infused in smaller volumes (100ml) over a shorter period of time (not less than 15 minutes). The Panel thus considered that Zometa could be administered quickly; there was no implication from the claim in question that 'quick' referred to a bolus injection. No breach of Clause 7.2 was ruled in that regard.

The Panel considered that the claim that Zometa was convenient to use implied an advantage over other similar therapies. This was not so. As with other intravenous bisphosphonates, patients had to have their renal function and plasma electrolytes measured. Prescribers must also ensure that patients treated with Zometa were adequately hydrated. This was not the case for other bisphosphonates. The Panel considered that Zometa was no more convenient to administer than other bisphosphonates and in that regard the implied advantage was misleading. A breach of Clause 7.2 was ruled.

APPEAL BY NOVARTIS

Novartis noted that Zometa was given by 15 minute intravenous infusion every 3 – 4 weeks for bone metastases. Many of these patients would be attending outpatient clinics regularly to receive chemotherapy and would receive Zometa at the same time. Ensuring that such patients were adequately hydrated before giving a dose of Zometa would take a member of the medical team a matter of seconds, and so Novartis did not consider that this alone singled Zometa out from other intravenous bisphosphonates.

Section 4.4 of all bisphosphonate SPCs recommended monitoring of renal function during treatment as follows:

Bondronat (ibandronic acid) oral and IV: 'Nevertheless, according to clinical assessment of the individual patient, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with Bondronat'.

Loron 520 (clodronate, oral): 'It is recommended that appropriate monitoring of renal function with serum creatinine be carried out during treatment'.

Bonefos (clodronate) oral and IV: 'It is recommended that appropriate monitoring of renal function with

serum creatinine measurement be carried out during treatment'.

Aredia (pamidronate): 'As with other i.v. bisphosphonates renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of Aredia'.

Zometa: 'As with other bisphosphonates renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of Zometa'.

In terms of 'convenience' therefore, Zometa had similar requirements for monitoring of renal function as other bisphosphonates, both oral and IV and had the advantage over other IV preparations of a considerably shorter infusion time (15 minutes versus 1-2 hours). Efficacy issues apart, this must be weighed against the 'convenience' of oral preparations which could obviously be taken at home, once or twice a day (versus once every 3-4 weeks), but all of which required a variable fast beforehand (due to poor absorption) and the patient to remain upright for a time after dosing (to avoid oesophageal ulceration).

Novartis did not consider that the claim 'Zometa is quick and convenient to administer' was inappropriate as it did not imply that it was more or less convenient than other bisphosphonates, only that it was convenient. The company denied a breach of Clause 7.2 with regard to 'convenient'.

COMMENTS FROM ROCHE

Roche stated that Novartis was incorrect to state that 'Zometa had similar requirements for monitoring of renal function as other bisphosphonates'. Novartis had omitted the preceding sentence to its cited quotation from the Bondronat SPC, ie 'Clinical studies have not shown any evidence of deterioration in renal function with long term Bondronat therapy'. This omission altered and misled the context of the subsequent monitoring statement.

Roche noted that Zometa must be withheld 'if renal function has deteriorated'. The only way to ensure that was the accepted practice of testing renal function before every dose of Zometa. This was not a requirement of IV or oral Bondronat, where routine renal function tests occurred as part of the overall management of a patient with metastatic bone disease and were not dictated before every dose. The American Society of Clinical Oncology (ASCO) panel recommended that: 'serum creatinine should be monitored prior to each dose of pamidronate or zoledronic acid' and recognised that 'it may be difficult or inconvenient for some clinics to obtain results of renal function tests before pamidronate or zoledronic acid administration' and recommended that 'the FDA-approved monitoring guidelines be followed.' The ASCO panel also noted: 'A time and motion study at three outpatient chemotherapy infusion sites participating in the zoledronic acid vs pamidronate clinical trial found an average visit time for zoledronic acid patients was 1 hour 6 minutes … .'

Roche questioned the convenience of a patient having Zometa therapy withheld (and hence, losing the benefits of continued treatment of their metastatic bone disease). IV medicines carried inherent safety requirements that did not make them convenient for a patient when oral, at home, alternative medicines might be available. In addition, it was not convenient to have to exercise caution 'when Zometa is used with other potentially nephrotoxic agents.' Roche alleged that the claim was misleading in breach of Clause 7.2.

APPEAL BOARD RULING

The Appeal Board did not consider that, within the overall context of treating a patient with cancer, Zometa would be seen as inconvenient. Zometa could be administered by a 15 minute infusion, which was faster than other IV bisphosphonates. The Appeal Board considered that this advantage was in itself a convenient aspect of Zometa therapy. The Appeal Board did not consider that the claim was misleading and no breach of Clause 7.2 was ruled. The appeal on this point was successful.

14 Claim 'Zometa is well tolerated'

This claim was the headline on page 12 of the detail aid.

COMPLAINT

Roche stated that of all the issues raised by this detail aid, the fact that Novartis had not fully informed prescibers about the issues surrounding Zometa and renal toxicity was of greatest concern. Renal toxicity was described as 'common' in the Zometa SPC and yet was not even mentioned in the detail aid which gave prominence to details only of efficacy.

References were not made to the letter to the New England Journal of Medicine (Chang *et al* 2003) from the Food and Drug Administration (FDA) discussing renal toxicity concerns about zoledronic acid. Roche noted that no such concerns were raised in this FDA letter about any other bisphosphonates. Other publications had cited and discussed Zometa's renal toxicity (Markowitz *et al* 2003 and Johnson *et al* 2003).

No reference was made to the important safety requirement of withholding treatment with Zometa if patients had severe renal impairment. The obligation to discontinue therapy put the patient at further risk of skeletal events in the absence of bisphosphonate cover from Zometa.

No mention was made of the need for caution with the use of Zometa with other potentially nephrotoxic agents. Co-morbidities and concomitant medications were becoming an increasingly important consideration in the management of patients with advanced cancers, especially the elderly.

Roche noted that Novartis had failed to give due emphasis to these important safety matters when discussing safety issues on page 12 in breach of Clause 7.2 in being unbalanced and misleading. As withholding vital safety data put patients at potential risk, Roche considered that the Panel might view this seriously enough to constitute a breach of Clause 2.

RESPONSE

Novartis submitted that Zometa was considered to be well tolerated, notwithstanding the fact that it was used in cancer patients. The trial data for Zometa consistently showed that the adverse event profile was similar to pamidronate or placebo.

Novartis noted Roche's submission with regard to renal function and the Zometa SPC and stated that the SPC reflected its marketing authorization and its position with regard to the relevant competent authorities, in this case the European Medicines Evaluation Agency (EMEA). Several adverse events were listed in Section 4.8 as occurring 'commonly' and indeed 'very commonly', but none was given particular prominence, and none was subject to any warning issued by the Medicines Commission, the Committee on Safety of Medicines (CSM) or the EMEA. Novartis noted that the statement on renal function read 'There have been some reports of impaired renal function (2.3%), although the aetiology appears to be multifactorial in many cases'.

Novartis was unclear therefore why Roche had mentioned just one adverse event for particular scrutiny although it cited Chang *et al* from the FDA. Novartis explained that this letter to the editor was neither an FDA letter nor an official FDA position, and contained only information which was consistent with the US package insert and the UK SPC for Zometa. It added no new information and Novartis had not been asked to amend the wording of either its US or European marketing authorizations as a result.

Novartis noted that the prescribing information on the back page of the detail aid listed all the adverse events that appeared in Section 4.8 of the SPC. The company submitted that it had neither misled the reader nor withheld vital safety data. Breaches of Clauses 7.2 and 2 were denied.

PANEL RULING

The Panel noted that the Zometa SPC stated that the product must only be used by clinicians experienced in the administration of intravenous bisphosphonates. In the Panel's view these physicians would be well aware that such medicines had to be used with care in patients with renal impairment and that renal function should be monitored during therapy. The Zometa SPC stated that the adverse reactions to the medicine were similar to those reported for other bisphosphonates and could be expected to occur in approximately one third of patients. The Panel did not consider that the omission of data regarding the renal toxicity of Zometa gave a misleading impression of the safety of the product. There was no implication that renal toxicity was not a problem with Zometa. The Panel thus considered that the claim 'Zometa is well tolerated' was not misleading. No breach of Clause 7.2 was ruled. The Panel consequently also ruled no breach of Clause 2 of the Code.

APPEAL BY ROCHE

Roche noted the Panel's statement '... these physicians would be well aware that such medicines had to be used with care in patients with renal impairment' but considered that one of the main functions of promotion was to inform prescribers. Roche disagreed with the Panel's assertion that 'the omission of data regarding the renal toxicity of Zometa [did not give] a misleading impression of the safety of the product'. There were special concerns about Zometa that were not common to all other bisphosphonates and page 12 of the detail aid on tolerability failed to bring this to the attention of that specialised audience.

Roche noted that renal toxicity was described as 'common' in the Zometa SPC and that Chang *et al* from the FDA had discussed renal toxicity concerns about zoledronic acid. No such concerns were raised in this letter about any other bisphosphonate. Other publications had cited and discussed Zometa's renal toxicity (Markowitz *et al* and Johnson *et al*). A new publication highlighted the increased risk of renal toxicity with zoledronic acid compared with pamidronate (Mazj *et al* 2004). There was an SPC safety requirement of withholding Zometa treatment if patients had severe renal impairment. The obligation to discontinue therapy put the patient at further risk of skeletal events in the absence of bisphosphonate cover from Zometa. Roche further noted that the Zometa SPC advised caution with the use of Zometa with other potentially nephrotoxic agents. Co-morbidities and concomitant medications were becoming an increasingly important consideration in the management of patients, especially elderly patients with advanced cancer.

Roche stated that whilst the majority of data in the detail aid related to efficacy, the tolerability page made only two tolerability claims – 'Zometa is well tolerated' and 'Adverse reactions to Zometa were comparable to those reported for pamidronate disodium or placebo'. This implied that all adverse effects were at a placebo level but did not reflect the prescribing information that stated 'Very common: Hypophosphataemia. Common: Anaemia, headache, conjunctivitis, nausea, anorexia, bone pain, myalgia, arthralgia, renal impairment, fever, flu-like syndrome, increased blood creatinine and blood urea, hypocalcaemia, generalised pain...'. Uncommon and rare undesirable effects were also listed. In addition, the pamidronate SPC also listed adverse events.

To imply that all adverse reactions were comparable to placebo failed to qualify the true profile of Zometa's and pamidronate's undesirable effects. It was misleading in breach of Clause 7.2. The campaign to minimise the emerging concern over the renal toxicity of Zometa was worthy of consideration of a breach of Clause 2.

COMMENTS FROM NOVARTIS

Novartis noted that Roche had stated that 'There were special concerns about Zometa that were not common to all bisphosphonates' and that page 12 of the detail aid on tolerability failed to bring this to the attention of the target audience.

Novartis disagreed that there were 'special concerns' about Zometa; as stated before, the SPC was not subject to any particular warnings issued by any of the regulatory bodies or the CSM. In addition Novartis had submitted regular Periodic Safety

Update Reviews on Zometa, and these had not led to any change in relation to the SPC wording about renal adverse events. In particular, in Section 4.8 the SPC stated: 'Adverse reactions to Zometa are similar to those reported for other bisphosphonates and can be expected to occur in approximately one third of patients' as noted by the Panel in its ruling. Thus Zometa did not appear to have 'special concerns' compared to other bisphosphonates.

Novartis noted that Roche had again cited the fact that renal toxicity was listed on the SPC as 'common', and that Chang *et al* as well as other publications referred to renal toxicity. Renal toxicity was listed in the SPC as common because it was present in 1-10% of patients in clinical trials, this was reflected in Section 4.8: 'There have been some reports of impaired renal function (2.3 %), although the aetiology appears to be multifactorial in many cases'. This statement had not been amended with the post-marketing experience of Zometa, and reflected the fact that the patients treated on the clinical trial programme, and subsequently, included some – particularly those with multiple myeloma – who might have had a multifactorial aetiology to their renal impairment. Chang *et al* stated nothing different – it recommended renal monitoring, adequate hydration and discontinuation of treatment with Zometa if renal deterioration occurred, exactly as in the SPC. The letter from Chang *et al* was not an official FDA position.

Novartis noted that Roche had also reiterated the SPC recommendations about not using Zometa in patients with severe renal impairment and also the use with potentially nephrotoxic agents. Neither of these statements negated the fact that Zometa was generally well-tolerated in a population of patients with advanced cancer.

Novartis noted that Roche had introduced a new element to its complaint citing, for the first time, the statement 'Adverse reactions to Zometa were comparable to those reported for pamidronate disodium or placebo'. Novartis understood that no new complaint could be introduced at this point in the process, and so it did not comment further on this aspect.

FURTHER COMMENTS FROM ROCHE

Roche stated that Novartis had incorrectly stated that the Zometa SPC was not subject to any particular warnings. Section 4.4 of the SPC (Special warnings and precautions for use) stated that Zometa 'should be withheld if renal function has deteriorated' and '… the use of Zometa is not recommended in patients with severe renal impairment'. This was not the case with Bondronat. Whilst the Zometa SPC might state that 'Adverse reactions to Zometa are similar to those reported for other bisphosphonates and can be expected to occur in approximately one-third of patients', this must be taken into context. 'Similar' did not mean identical. Bondronat was launched after Zometa in metastatic bone disease and this SPC statement now represented an historical perspective. It did not match the fact that clinically relevant renal toxicity was not a feature of Bondronat. The Bondronat SPC stated 'Clinical studies have shown no evidence of deterioration of renal function with long term Bondronat therapy'. Roche contrasted this with Novartis' admission of a 1-10% renal toxicity with Zometa trials.

Roche stated that Novartis had now tempered its claim; its new stated position was that 'Zometa is generally well tolerated'. This seemed to recognise that Zometa had tolerability concerns and supported Roche's appeal that the overall claim 'Zometa is well tolerated' was misleading.

Roche's stated that its comment on the claim that 'Adverse reactions to Zometa were comparable to those reported for pamidronate disodium or placebo' was not a new complaint but was cited to reflect the fact that this was falsely used to support the claim that 'Zometa is well tolerated'.

Roche was concerned that important patient safety information was not being shared with health professionals and there were sufficient SPC and published data to warrant these issues being fairly presented in promotion. Roche requested that the serious nature of suppressing such information be reconsidered. A breach of Clause 2 was alleged.

APPEAL BOARD RULING

The Appeal Board noted Roche's original complaint was that Novartis had not fully informed prescribers about the issues surrounding Zometa and renal toxicity. Further, that Novartis had failed to give due emphasis to important safety matters relating to renal toxicity on the page headed 'Zometa is well tolerated' and this was unbalanced and misleading.

The SPC stated that Zometa must only be used by clinicians experienced in the administration of IV bisphosphonates. In the Appeal Board's view these physicians would be well aware that such medicines had to be used with care in patients with renal impairment and that renal function should be monitored during therapy. The SPC stated that the adverse reactions to Zometa were similar to those reported for other bisphosphonates and could be expected to occur in approximately one third of patients. The Appeal Board noted that there were some concerns regarding the renal tolerability profile of Zometa but considered that these had been exaggerated by Roche. The Appeal Board did not consider that the failure to refer to the renal tolerability profile of the product rendered the claim 'Zometa is well tolerated' misleading and unbalanced as alleged. The Panel's rulings of no breach of Clauses 7.2 and 2 were upheld. The appeal on this point was unsuccessful.

During its consideration of this point the Appeal Board was concerned that the claim 'Zometa is well tolerated' was a broad, unequivocal and unqualified claim. The Appeal Board also noted that another claim on the same page stated that adverse reactions to Zometa were comparable to those reported for pamidronate or placebo. The Appeal Board considered these two claims implied minimal risk with Zometa and questioned whether this was so. The Appeal Board requested that Novartis be advised of its views in this regard.

15 Claim 'Zometa has a fast and convenient administration'

This claim appeared as the heading to page 13 and was referenced to the SPC.

COMPLAINT

Roche stated that the same issues arose here as in point 13 above regarding the claim 'Zometa is quick and convenient to deliver'. 'Fast' was a vague term. This word did not appear in the SPC and so it was in breach of Clause 7.5. The instructions as to how to administer Zometa which were given on page 13 also misled the reader in breach of Clause 7.2 as patients would require a pre-dose renal test to comply with the SPC requirement that 'Zometa is not recommended in patients with severe renal failure' and for 'the measurement of renal function prior to each dose. In all patients with bone metastases, the dose should be withheld if renal function has deteriorated'. The 'convenience' claim failed to take into account the need for pre-dose renal function testing and the whole inconvenience of attending hospital and/or receiving an intravenous infusion. This was misleading in breach of Clause 7.2.

RESPONSE

Novartis stated that as for point 13 above, it considered that most clinicians would accept that a 15 minute infusion was 'fast' and would understand what 'fast' meant. It was entirely consistent with the SPC and not in breach of Clause 7.5.

Novartis noted that the instructions on page 13 did not mislead the reader as the first step was to ensure that the patient had acceptable creatinine levels, as defined in the SPC, prior to administering each dose of Zometa. This was therefore not in breach of Clause 7.2.

As in point 13 above, the claim about convenience seemed entirely reasonable and not in breach in Clause 7.2.

PANEL RULING

The Panel noted that the claim at issue 'Zometa has a fast and convenient administration' headed page 13 which detailed the practicalities of administering the medicine. A claim at the bottom of the page compared the treatment time per infusion for pamidronate (152 minutes) and Zometa (59 minutes). The Panel noted its comments and rulings at point 13 above with regard to 'quick' and 'convenient' and considered that they applied here. The Panel thus ruled no breach of Clauses 7.2 and 7.5 with regard to fast and a breach of Clause 7.2 with regard to convenient.

APPEAL BY NOVARTIS

As for the claim in point 13 above, Novartis did not consider this to be in breach of Clause 7.2 with regard to 'convenient'.

COMMENTS FROM ROCHE

Roche referred to its comments at point B above.

APPEAL BOARD RULING

The Appeal Board noted its comments at point 13 above with regard to 'convenient' and considered that they applied here. The Appeal Board thus ruled no breach of Clause 7.2 of the Code. The appeal on this point was successful.

Complaint received **4 June 2004**

Case completed **6 October 2004**

VOLUNTARY ADMISSION BY BRISTOL-MYERS SQUIBB and OTSUKA

Abilify mailing

Bristol-Myers Squibb and Otsuka voluntarily advised the Authority that their mailing house had, in error, sent letters announcing the launch of Abilify (aripiprazole) before the marketing authorization had been received. The letters had been sent to 117 mental health pharmacists. Corrective action was taken immediately.

The Director of the Authority decided that as the matter related to the promotion of a medicine prior to the grant of the marketing authorization 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 it was an established principle under the Code that pharmaceutical companies were responsible for activities carried out by third parties with their authority. Bristol-Myers Squibb and Otsuka were thus responsible for the activities of their mailing house.

The explanation from the mailing house was that the box containing the mailing to the pharmacists had not been labelled 'hold' pending receipt of an instruction to despatch from Bristol-Myers Squibb and Otsuka. All the other boxes in the mailing had been so labelled. It appeared that the box containing the letters at issue fell off a pallet and was incorrectly placed with other items which were awaiting despatch. The mailing house apologised for the error and described the steps it had taken to ensure that there was no repeat.

The Panel noted that the companies had been let down by the mailing house resulting in a promotional letter being sent before the marketing authorization for Abilify had been granted. The Panel thus ruled a breach of the Code.

Bristol-Myers Squibb Pharmaceuticals Ltd and Otsuka Pharmaceuticals (UK) Ltd voluntarily advised the Authority that their mailing house had, in error, sent letters announcing the launch of Abilify (aripiprazole) before the marketing authorization had been received. The letters (ref ABL/04-04/0291c/03-06) had been sent to 117 mental health pharmacists. Corrective action was taken immediately.

The Director of the Authority decided that as the matter related to the promotion of a medicine prior to the grant of the marketing authorization 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 Bristol-Myers Squibb and Otsuka respond in relation to the provisions of Clause 3.1 of the Code.

RESPONSE

Bristol-Myers Squibb and Otsuka submitted a joint response and stated that the Commission of the European Communities granted the marketing authorization for Abilify to Otsuka Pharmaceuticals Europe Ltd on 4 June 2004. However, on 3 June a mental health pharmacist contacted Bristol-Myers Squibb's medical information department, to discuss the availability of Abilify. The pharmacist had received the letter in question. The medical information department immediately alerted Bristol-Myers Squibb, Otsuka and the mailing house. An outline plan for corrective action was verbally agreed.

The mailing house confirmed that it had sent the mailing in error to 117 mental health pharmacists on 2 June, despite a written instruction to ensure all such materials were to be held until released by the companies upon receipt of the marketing authorization. On 4 June the mailing house wrote to Otsuka and Bristol-Myers Squibb confirming the error on its part and stating that it accepted full responsibility as a result of the failure of its procedure. A copy of the letter sent by the mailing house was supplied.

Bristol-Myers Squibb and Otsuka instigated and implemented a strategy to contact the 117 mental health pharmacists as a matter of urgency starting on Friday, 4 June. The companies realised the seriousness and potential for breaching the Code and telephoned the Authority for guidance and then subsequently made a voluntary admission. The companies also informed the Medicines and Healthcare products Regulatory Agency as the matter was of the utmost importance.

Bristol-Myers Squibb and Otsuka gave the mailing house a telephone script to use to contact the mental health pharmacists. This was to enable the mailing house to obtain fax numbers or email addresses for the relevant pharmacists. A letter of apology was then faxed/emailed. One hundred and one people were faxed/emailed on 4 June or over the weekend. Unfortunately sixteen people could not be contacted due to eight fax machines not working and eight people not being contactable by phone.

A letter of apology was mailed to all 117 pharmacists on 4 June 2004.

Also on 4 June all relevant customer facing personnel were informed of the mailing error. They were briefed on how to respond to questions from pharmacists as a result of the premature mailing about the marketing authorization.

On 8 June Bristol-Myers Squibb and Otsuka expressed their extreme dissatisfaction to the mailing house at

the failure of the service, sought assurance that nothing of that kind would occur again and requested details of the full review of the processes put in place to prevent any such future occurrences. On 22 June a letter was received from the mailing house explaining the results of its investigation into the error and identifying improvements to the processes to prevent any repetition.

The companies submitted that the premature notification of the Abilify marketing authorization was made to only a small group of pharmacists by the mailing house. Neither Bristol-Myers Squibb nor Otsuka had intended that this should occur, and both companies had taken all reasonable precautions to prevent such an erroneous notification. The companies regretted that the mailing house's error had inadvertently caused the companies to breach the Code.

PANEL RULING

The Panel noted that it was an established principle under the Code that pharmaceutical companies were responsible for activities carried out by third parties with their authority. Bristol-Myers Squibb and Otsuka were thus responsible for the activities of their mailing house.

The explanation from the mailing house was that the box containing the mailing to the pharmacists had not been correctly labelled 'hold' pending receipt of an instruction to despatch from Bristol-Myers Squibb and Otsuka. All the other boxes in the mailing had been so labelled. It appeared that the box containing the letters at issue fell off a pallet and was incorrectly placed on a pallet of other items which were awaiting despatch. The mailing house apologised for the error and described the steps it had taken to ensure that such an error was not repeated.

The Panel noted that the companies had been let down by the mailing house resulting in a promotional letter being sent to 117 pharmacists before the marketing authorization for Abilify had been granted. The Panel thus ruled a breach of Clause 3.1 of the Code.

Proceedings commenced 15 June 2004

Case completed 27 July 2004

CASE AUTH/1598/6/04

GLAXOSMITHKLINE CONSUMER HEALTHCARE v PFIZER CONSUMER HEALTHCARE

Nicorette Patch journal advertisement

GlaxoSmithKline Consumer Healthcare complained about an advertisement for Nicorette Patch issued by Pfizer Consumer Healthcare, which was headed 'Nicorette patch can protect patients from unnecessary sleep disturbance' and featured an illustration of a woman asleep in bed beneath which was a person dressed as a cigarette. Text beneath the illustration started 'Because Nicorette 16 hour Patch is the only patch specifically designed to mimic your patient's regular smoking pattern, it avoids the nocturnal nicotine dosing often associated with sleep disturbance. In fact, Nicorette 16 hour Patch is the only one not shown to increase levels of sleep disturbance over and above placebo levels'. Nicorette patches released nicotine over 16 hours; GlaxoSmithKline Consumer Healthcare marketed NiQuitin CQ Patches which delivered nicotine over 24 hours.

GlaxoSmithKline Consumer Healthcare stated that the advertisement implied that patients on Nicorette would get a good night's sleep, and those using 24-hour patches would not. Neither of these impressions was necessarily correct. The impression of Nicorette giving patients a good night's sleep was created by the visual of a woman sleeping peacefully in bed. The word 'unnecessary' in the headline did not negate this impression, and neither did the phrase 'not shown to increase levels of sleep disturbance over and above placebo levels' as no mention was made that nicotine withdrawal itself could cause sleep disturbance. Waking once or twice might be equivalent to placebo but did not constitute a good night's sleep. Any material discussing sleep disturbance in smoking cessation should make it explicitly clear that nicotine withdrawal itself could cause sleep disturbance so that readers were not misled. A breach of the Code was alleged.

A further breach of the Code was alleged as the advertisement failed to state that the prescribing information appeared overleaf.

The Panel did not consider that the advertisement adequately distinguished between sleep disturbance caused by the treatment and that caused by the lack of nicotine. The advertisement noted that nocturnal nicotine dosing was often associated with sleep disturbance but did not state that nicotine withdrawal *per se* was also associated with sleep disturbance. The claim that Nicorette did not 'increase levels of sleep disturbance over and above placebo levels' was not sufficient in this regard. Some readers would assume that placebo levels of sleep disturbance meant none. There was thus an implication that patients using Nicorette would sleep well whereas their sleep patterns would still be disrupted due to nicotine withdrawal. The Panel noted that Nicorette, however, would not add to this effect. Nonetheless, the Panel considered that the advertisement gave a misleading impression of the sleep pattern that might be expected in a patient using Nicorette. A breach of the Code was ruled.

The Panel noted that the advertisement was a two page advertisement with the prescribing information appearing overleaf. There was no reference on the first page as to the location of the prescribing information as required by the Code and a breach was ruled.

GlaxoSmithKline Consumer Healthcare complained about a journal advertisement for Nicorette Patch (transdermal nicotine) issued by Pfizer Consumer Healthcare Limited. The advertisement appeared in MIMS, June 2004. The advertisement, which did not have a reference number, was headed 'Nicorette patch can protect patients from unnecessary sleep disturbance' and featured an illustration of a woman asleep in bed beneath which was a person dressed as a cigarette. The text beneath the illustration started 'Because Nicorette 16 hour Patch is the only patch specifically designed to mimic your patient's regular smoking pattern, it avoids the nocturnal nicotine dosing often associated with sleep disturbance. In fact, Nicorette 16 hour Patch is the only one not shown to increase levels of sleep disturbance over and above placebo levels'.

Nicorette patches released nicotine over 16 hours' use. GlaxoSmithKline Consumer Healthcare marketed NiQuitin CQ Patches (transdermal nicotine) which delivered nicotine over 24 hours.

COMPLAINT

GlaxoSmithKline Consumer Healthcare noted that its recent complaint about an advertisement for Nicorette Patch (Case AUTH/1563/3/04) had been upheld by the Panel. The Panel did not consider the claim 'helps your patients avoid the nocturnal nicotine dosing associated with unnecessary sleep disturbance' adequately distinguished between the two types of sleep disturbance [sleep disturbance that was part and parcel of quitting, and that caused by nocturnal nicotine dosing] and considered some readers would be left with the impression that those taking Nicorette would not have a disturbed night's sleep and this was not necessarily so as they would continue to experience the sleep disruption caused by nicotine withdrawal. The footnote 'Nicorette 16 hour Patch is the only one not shown to cause sleep disturbance over and above placebo levels' did not negate the impression given. The expectation of a good night's sleep was strengthened by the visual of a woman sleeping peacefully in bed. A breach of Clause 7.2 was ruled.

GlaxoSmithKline Consumer Healthcare stated that Pfizer Consumer Healthcare had replaced the advertisement at issue in Case AUTH/1563/3/04 with one used previously and which GlaxoSmithKline Consumer Healthcare had previously alleged was in breach of the undertaking given in Case AUTH/1329/6/02. The alleged breach of undertaking was considered as Case

AUTH/1380/10/02 and the Panel ruled that the undertaking given in Case AUTH/1329/6/02 had not been breached because the advertisement was sufficiently different from that considered in Case AUTH/1329/6/02. However, this did not necessarily mean that the Panel approved the advertisement at issue in Case AUTH/1380/10/02. Therefore GlaxoSmithKline Consumer Healthcare asked the Authority to consider its concerns in this case, [Case AUTH/1598/6/04], as a complaint rather than a breach of undertaking.

GlaxoSmithKline Consumer Healthcare stated that the current advertisement implied that patients on Nicorette would get a good night's sleep, and those using 24-hour patches would not. Neither of these impressions was necessarily correct. The impression of Nicorette giving patients a good night's sleep was created at the outset by the visual of a woman sleeping peacefully in bed. The use of the word 'unnecessary' in the headline did not negate this impression, and neither did use of the phrase 'not shown to increase levels of sleep disturbance over and above placebo levels' as no mention was made that nicotine withdrawal itself could cause sleep disturbance. Waking once or twice in the night might be equivalent to placebo but did not constitute a good night's sleep. Any material discussing sleep disturbance in smoking cessation should make it explicitly clear that smoking cessation (ie nicotine withdrawal) itself could cause sleep disturbance so that readers were not misled. A breach of Clause 7.2 was alleged.

GlaxoSmithKline Consumer Healthcare also alleged a breach of Clause 4.7 as the advertisement failed to state that the prescribing information appeared overleaf.

RESPONSE

Pfizer Consumer Healthcare stated that the complaint was a surprise as the company had not placed this advertisement; had it realised that the advertisement had run, it would have made an immediate voluntary disclosure to the Authority. Unfortunately the letter from the Authority notifying the company of the complaint was the first Pfizer Consumer Healthcare knew of this.

MIMS confirmed that the advertisement ran because of an administrative error involving MIMS' internal booking systems. MIMS had not received a booking for or authority to run the advertisement from either Pfizer Consumer Healthcare or its booking agency. Pfizer Consumer Healthcare would not be paying for the advertisement.

Whilst Pfizer Consumer Healthcare recognised that under the Code it was responsible for the advertisement, it hoped to provide evidence of mitigating circumstances and there was absolutely no intention to breach the Code.

Pfizer Consumer Healthcare apologised unreservedly for the erroneous placement of this unapproved advertisement. Nevertheless the company stood by the advertisement.

Pfizer Consumer Healthcare submitted that the visual was appropriate since it drew attention to the topic under discussion: sleep. It did not imply no sleep disturbance, in the same way that an image of a smiling man in an asthma product advertisement did not imply that the product would relieve all symptoms of asthma.

There had never been any intention to mislead the sophisticated health professional audience who would understand the phrase 'has not been shown to increase levels of sleep disturbance over and above placebo levels' to mean that sleep disturbance was part and parcel of quitting smoking (placebo group) and would not be exacerbated by a 16-hour patch which was intended for removal at bedtime (Nicorette).

Pfizer Consumer Healthcare submitted that its response to Case AUTH/1380/10/02 answered GlaxoSmithKline Consumer Healthcare's complaint.

> 'Again based on the data provided for the previous ruling, [Case AUTH/1329/6/02] the Panel accepted that several studies had shown that sleep disturbances were not reported more frequently in patients using an active 16-hour patch compared to placebo. The Panel also agreed that 16-hour patches did not cause sleep disturbances *per se*. In addition, as a simple statement of fact, Nicorette Patch was the only 16-hour patch; all other patches were designed for 24-hour administration. The Panel's ruling stated that sleep disturbance during smoke cessation could also be caused by night-time dosing if a patient used a 24-hour patch. The company therefore understood that the Panel accepted the data provided for the previous ruling which showed the increased incidence of sleep disturbances with 24-hour patches when compared to placebo and that insomnia and abnormal dreams were listed as potential adverse effects with NiQuitin CQ patches whereas they were not listed for Nicorette Patch.
>
> In the previous case, the issue was that the company had not made it clear that there could be sleep disturbances as a consequence of nicotine withdrawal. However the headline 'Nicorette Patch can protect patients from unnecessary sleep disturbance' made it clear that the subject of the advertisement was avoidable sleep disturbances. This was supported by the amended statement which did not claim that there were no sleep disturbances but that there was no increase in sleep disturbances over placebo levels using 16-hour patches. This was in contrast to 24-hour patches where the Panel accepted that nocturnal nicotine dosing can cause sleep disturbances over placebo levels'.

Pfizer Consumer Healthcare noted the absence of a unique reference number on the advertisement and the absence of a reference to the location of the prescribing information.

PANEL RULING

The Panel was curious with regard to what it saw as an inconsistency in Pfizer Consumer Healthcare's

submission that had it known the advertisement had appeared it would have made a voluntary admission and that Pfizer Consumer Healthcare stood by its advertisement.

The Panel noted that the advertisement now at issue was similar to that at issue in Case AUTH/1380/10/02. The text and illustration were the same although the layouts were different.

In Case AUTH/1329/6/02 the Panel had ruled breaches of the Code as claims such as 'For patients who want to give up smoking, not their sleep', '… by avoiding the nocturnal nicotine dosing commonly associated with sleep disturbance – …' and 'In fact when compared to placebo Nicorette 16 hour Patch is the only nicotine patch which has not been shown to cause sleep disturbance' in the context of the advertisement as a whole gave the impression that patients using Nicorette patch would not suffer sleep disturbance at all. This was not necessarily so.

The advertisement subsequently at issue in Case AUTH/1380/10/02 had been ruled not to be in breach of the undertaking given in Case AUTH/1329/6/02. The Panel had considered that the advertisement was sufficiently different; it referred to minimising the risk of unnecessary sleep disturbance whereas the advertisement in Case AUTH/1329/6/02 implied that patients using Nicorette Patch would not suffer sleep disturbance at all. Such patients would not avoid the sleep disturbance caused by lack of nicotine.

The Panel noted that in Case AUTH/1563/3/04 it had ruled a breach with regard to the claim '[Nicorette] helps your patients avoid the nocturnal nicotine dosing commonly associated with unnecessary sleep disturbance' as it did not adequately distinguish between the two types of sleep disturbance.

Turning to the case now before it, Case AUTH/1598/6/04, the Panel noted that the advertisement had appeared in error. Nonetheless Pfizer Consumer Healthcare had to take responsibility for it under the Code.

The Panel did not consider that the advertisement adequately distinguished between two types of sleep disturbance, that caused by the treatment and that caused by the lack of nicotine. The advertisement noted that nocturnal nicotine dosing was often associated with sleep disturbance but did not state that nicotine withdrawal *per se* was also associated with sleep disturbance. The claim that Nicorette did not 'increase levels of sleep disturbance over and above placebo levels' was not sufficient in this regard. Some readers would assume that placebo levels of sleep disturbance meant none. There was thus an implication that patients using Nicorette would sleep well whereas their sleep patterns would still be disrupted due to nicotine withdrawal. The Panel noted that Nicorette, however, would not add to this effect. Nonetheless, the Panel considered that the advertisement gave a misleading impression of the sleep pattern that might be expected in a patient using Nicorette. A breach of Clause 7.2 of the Code was ruled.

The Panel noted that the advertisement was a two page advertisement with the prescribing information appearing overleaf. There was no reference on the first page as to the location of the prescribing information as required by Clause 4.7. A breach of that clause was ruled.

Complaint received **23 June 2004**

Case completed **9 August 2004**

CASE AUTH/1599/6/04

NOVARTIS v ROCHE

Press articles about Bondronat

Novartis complained about various articles which had appeared in the medical and lay press about Roche's product Bondronat (ibandronate).

Bondronat was available as film-coated tablets and as a concentrate for solution for intravenous administration (IV). Both presentations were indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. In addition Bondronat IV was also indicated for the treatment of tumour-induced hypercalcaemia with or without bone metastases. Novartis marketed Zometa (zoledronic acid) which had similar indications to Bondronat. Both products belonged to a class of medicines known as bisphosphonates.

Novartis alleged that the claim 'Oral treatment for metastatic bone disease' in an article in Prescriber and Future Prescriber was misleading as Bondronat tablets were only licensed for patients with breast cancer and bone metastases, not other malignant types.

The Panel considered that the claim 'Oral treatment for metastatic bone disease' implied that Bondronat could be used to treat the metastases *per se* and that was not so. The Panel noted, however, that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself.

The Panel thus examined the material provided to the medical media. The 'Bondronat UK Launch – Pitch Points' document featured nine bullet points: the first introduced Bondronat as part of the management of advanced breast cancer. This was the only bullet point to refer to 'breast cancer', all of the others referred only to 'cancer'. The seventh point described Bondronat as the 'bone saver' which worked by 'effectively slowing the cancer's growth in the bone'. 'Metastatic Bone Disease – Background Information' described the pathophysiology, incidence, risk factors, complications, symptoms and goals of metastatic bone disease management. One goal of metastatic bone disease management was 'ideally, reduce disease progression and improve patient survival'. Although the document concluded by discussing metastatic bone disease and breast cancer this aspect was not mentioned at the beginning of the document, in the heading or such like. The backgrounder on Bondronat discussed the medicine's mode of action, licensed indications, administration, tolerability and the convenience of oral versus IV presentations. The document explained that 'Bondronat [was] licensed for treatment of tumour-induced hypercalcaemia of malignancy with or without metastases. Prevention of skeletal events in patients with breast cancer and bone metastases'. The section detailing the administration of Bondronat stated 'Bondronat is available as intravenous and oral formulations for the treatment of metastatic bone disease' and that 'For oral use the recommended dose for metastatic bone disease is 50mg once daily'. The document concluded that Bondronat provided 'an important clinical alternative for the treatment of bone metastases'. The medical media release 'Improving quality of life for advanced breast cancer patients with "bone saver"' discussed treatment of metastatic bone disease in breast cancer patients and explained that the 'bone saver' worked by inhibiting the spreading cancer from growing or multiplying in the bone and therefore reduced bone pain and bone fractures.

The Panel considered that overall the material directed at the medical press, apart from the medical media release 'Improving quality of life for advanced breast cancer patients with "bone saver"', did not make it sufficiently clear that although Bondronat was licensed for metastatic bone disease it was only for metastatic bone disease secondary to breast cancer. It was not licensed to treat metastatic bone disease resulting from any other cause. The Panel considered that the 'Pitch Points' document, the Bondronat backgrounder and the Metastatic Bone Disease – Background Information document were misleading in this regard and inconsistent with the particulars listed in the Bondronat summary of product characteristics (SPC). Breaches of the Code were ruled. The Panel considered that this ruling also applied to similar claims which appeared in DGNews.

Novartis alleged that the claim 'The oral formulation has equivalent efficacy to the IV drug' was misleading as there had been no direct comparisons of the two formulations. Any comparisons made were indirect and inferred.

The Panel considered that the 'Bondronat UK Launch – Pitch Points' document, the Bondronat backgrounder and the medical media release gave the impression that a direct clinical comparison of IV and oral Bondronat had proven that the two were equally effective and that was not so. The materials were misleading in this regard. A breach of the Code was ruled.

Novartis alleged that the absolute statement 'There are also no adverse renal effects …' was untrue since Section 4.8 of the SPC stated that azotaemia (uraemia) had been reported, albeit rarely; the claim was therefore misleading, inconsistent with the terms of the marketing authorization and misled as to the side effect profile of the medicine.

The Panel noted that a section entitled 'What are the side effects with Bondronat' within the Bondronat backgrounder began by discussing the toxicities associated with current bisphosphonates which, it was stated, could limit their clinical benefit. The first of three bullet points read 'infusion of pamidronate and zoledronate can lead to renal toxicity, which, in rare cases, can have severe and life-threatening consequences'. Product labelling and monitoring of patients taking zoledronate was discussed. The safety profile of oral Bondronat was described as 'comparable to placebo'. The Panel

considered that the section 'What are the side effects with Bondronat' implied that although renal toxicity had been reported in association with pamidronate and zoledronate none had been reported with Bondronat and that was not so. The medical media release stated that Bondronat had not been associated with increases in renal toxicity or renal adverse events.

The Panel noted that Section 4.8 of the Bondronat tablet SPC listed uraemia as an uncommon adverse event, occurring at a frequency of <1% compared with placebo. The Panel thus considered that the Bondronat backgrounder and the medical media release were misleading with regard to the renal side effects of Bondronat and the Panel ruled a breach of the Code with respect to both. The Panel did not consider that the matter warranted a ruling of a breach of Clause 2. The Panel considered that these rulings applied to a similar claim in EMIMS, April 2004.

Novartis alleged that the claim '… and the gastrointestinal side-effects of the oral formulation were comparable to placebo' was untrue and at odds with Section 4.8 of the SPC which listed dyspepsia, nausea, abdominal pain and oesophagitis, all of which were gastrointestinal side-effects which were reported commonly and greater than placebo. Novartis alleged that the claim was misleading and potentially risked patient safety.

The Panel noted that the oral Bondronat SPC listed, *inter alia*, dyspepsia, nausea, abdominal pain and oesophagitis as events reported more commonly than with placebo. A section of the Bondronat backgrounder entitled 'What are the side effects with Bondronat' discussed the side effects of other bisphosphonates which had limited their clinical benefit. The third bullet point read 'administration of oral clodronate can cause gastrointestinal disturbances …'. The section concluded with a discussion of Bondronat's side-effect profile, stating, *inter alia*, that the safety profile of Bondronat was comparable to placebo. Overall, the section implied that Bondronat would not cause gastrointestinal disturbance which was not so. The Panel considered that the Bondronat backgrounder was not a fair reflection of the SPC on this point and was thus misleading. A breach of the Code was ruled. The Panel did not consider that the matter warranted a ruling of a breach of Clause 2.

Novartis alleged that the claim which appeared in a DGNews item that 'Bondronat was also well tolerated, with patients experiencing adverse events similar to those in the placebo group' was similar to its allegation above with regard to the claims 'There are no adverse renal effects' and '… and the gastrointestinal side-effects of the oral formulation were compared to placebo'.

The Panel noted that the DGNews item referred almost exclusively to the publication that day of Body *et al* (2004). In its complaint Novartis had not quoted the whole of the claim which read, in full: 'Bondronat was also well tolerated, with patients experiencing adverse events similar to those in the placebo group with the exception of a small number of patients experiencing mild to moderate gastro-intestinal side effects'. Given the context of the news item it was clear that the claim at issue related only to the findings of one study. The Panel considered that the claim was a fair and accurate reflection of Body *et al* (2004). Given that the claim clearly related to only one cited study the Panel ruled no breach of the Code. It thus followed that there was no breach of Clause 2 of the Code.

With regard to the claim 'The oral drug has advantages over its competitor in that it is a small tablet taken only once daily' in Future Prescriber, Novartis assumed that the competitor was oral clodronate, but took issue with the fact that being a small tablet, or being taken once daily offered advantages. Bondronat tablets must be taken after an overnight fast (at least 6 hours) and before the first food or drink of the day and fasting should be continued for at least 30 minutes after taking the tablet. Conversely, Loron capsules might be taken after only an hour's fast. Loron might also be taken once daily. Novartis alleged that the claim was misleading.

The article in Future Prescriber referred to clodronate and zoledronic acid; both were competitors to Bondronat. Zoledronic acid (Zometa) was only available as an IV formulation and so the Panel assumed that the competitor referred to in the claim at issue was clodronate.

The Panel noted that both the medical media release and the Bondronat backgrounder stated that Bondronat was to be taken once daily. The Bondronat backgrounder additionally noted that Bondronat was a small tablet. Neither document referred to the size of clodronate tablets nor to their frequency of administration. None of the materials compared the tablet size or frequency of administration of Bondronat with clodronate; no breach of the Code was ruled.

Novartis noted that the Code allowed advance notification of new indications to budget holders for planning purposes. However, Novartis alleged that the readership of Future Prescriber could not be assumed only to fulfil the criteria of budget holders; many would be prescribers. Thus to give information to journalists about unlicensed indications constituted a breach of the Code. Novartis drew attention to a particular claim in Future Prescriber about ongoing trials in unlicensed indications.

The Panel noted that none of the press materials provided by Roche referred to ongoing or future trials with Bondronat in unlicensed indications. No breach of the Code was ruled.

Novartis alleged that the claims 'There is now a drug that could help such women to lead relatively normal lives' and 'One of the other benefits of Bondronat is that it is the first drug in its class – the so-called bisphosphonates – that can be taken orally without the need for regular intravenous injections or infusions in hospital' appeared in an article entitled 'A Pain-Free Future' in The Times newspaper were misleading. They implied that no such medicine was available previously which was

clearly inaccurate, since several bisphosphonates, both oral and IV were already available for treatment of breast cancer metastatic to bone. Loron had been available orally for some time. This should have been made clear in any briefing, in particular to the lay press.

The Panel noted that the consumer media release stated that Bondronat was 'the first and only treatment of its kind to be available in IV and oral formulations, with the same efficacy …'. The Panel considered that it was unclear as to what 'first' referred to ie 'treatment of its kind', 'available in IV and oral' or 'with the same efficacy'. The consumer media release was ambiguous and misleading as to the 'first' that Bondronat represented. A breach of the Code was ruled.

With regard to the claims '… Bondronat, which was originally developed as a treatment for osteoporosis …' and 'As a drug for osteoporosis, …' which appeared in The Times, Novartis alleged that as Bondronat was not licensed for osteoporosis these were in breach of the Code since the introduction of a new medicine must not be made known to the general public until the medical and pharmaceutical professions had been informed of its availability, which was clearly not so.

The Panel noted that none of the press materials provided referred to Bondronat and osteoporosis. The Panel thus ruled no breach of the Code.

With regard to the claim '… a frontline treatment to prevent cancer spreading beyond the breast' which appeared in The Times, Novartis referred to its allegation above.

The Panel noted that the statement in The Times article read, 'Bondronat … could also have a more important impact as a frontline treatment to prevent cancer spreading beyond the breast'. The claim thus referred to a possible future use of Bondronat. The Panel noted its comments above that none of the materials provided by Roche referred to ongoing or future trials with Bondronat in unlicensed indications. The Panel ruled no breach of the Code.

Novartis alleged that since Bondronat was not licensed for this indication, the claim 'If secondary cancer could be prevented, then many patients could stay disease-free' raised unfounded hopes and was in breach of the Code.

The Panel noted that the claim was a quotation from a medical oncologist. The quotation was not included in any of the Bondronat press materials provided by Roche and nor was there any reference to the particular medical oncologist. The Panel ruled no breach of the Code.

Novartis alleged that as Bondronat was not licensed for breast cancer, the title 'New breast cancer drug' of an article in Bella was in breach of the Code.

The Panel did not consider that any of the press materials provided by Roche gave the impression that Bondronat was licensed to treat breast cancer. No breach of the Code was ruled.

Novartis drew attention to the claim 'Ibandronic acid (brand name Bondronat) is the first and only treatment of its kind proven to offer patients up to two years relief from the often severe and disabling pain …' appeared in Bella and referred to a previous allegation.

The Panel noted that the claim at issue was similar to a statement in the consumer media press release. However, the Panel noted that Novartis had only referred to its previous allegation it had not made any other specific comment on what was a different claim to that previously considered. Similarly Roche had only referred to its previous response on a different claim. The Panel decided that in the light of the complaint and the response it had no choice other than to rule no breach of the Code.

Novartis Pharmaceuticals UK Ltd complained about various articles which had been published about Bondronat (ibandronate) which was marketed by Roche Products Limited.

Bondronat was available as film-coated tablets and as a concentrate for solution for intravenous administration (IV). Both products were indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. In addition Bondronat IV was also indicated for the treatment of tumour-induced hypercalcaemia with or without bone metastases.

Novartis marketed Zometa (zoledronic acid) which had similar indications to Bondronat. Both products belonged to a class of medicines known as bisphosphonates.

A Prescriber 5 April 2004 and Future Prescriber, Spring 2004

Articles in these two publications entitled 'Oral treatment for metastatic bone disease' announced the launch of Bondronat and discussed efficacy and tolerability data.

1 Headline 'Oral treatment for metastatic bone disease'

COMPLAINT

Novartis alleged that this headline claim was misleading as Bondronat tablets were only licensed for patients with breast cancer and bone metastases, not other malignant types. Whilst this might be a misinterpretation by the journal in question, it could represent breaches of Clauses 7.2 and 3.2.

RESPONSE

Roche described its media materials and explained that these were part of an awareness campaign as commonly employed by pharmaceutical companies at the time of a product launch. The materials provided to the media were:

- 'Metastatic Bone Disease – Background Information', Certified for use at a media briefing event in the UK on 21 November 2003.
- Medical media release entitled 'Improving quality of life for advanced breast cancer patients with

"bone saver"'. Certified for use as a media briefing document and embargoed until 10 March 2004.

- Consumer media release entitled 'Improving quality of life for advanced breast cancer patients with "bone saver"' Certified for use as a media briefing document and embargoed until 10 March 2004.
- 'Backgrounder – Bondronat (ibandronic acid)', certified for use as a media briefing document on 8 January 2004 and available as required.
- 'Bondronat UK Launch – Pitch Points' used verbally with journalists

Roche explained that it contacted journalists via its UK public relations department. One of the journalists might have been briefed at an international cancer meeting by Roche's international colleagues. Discussions would also have occurred with the investigators and authors of the key published trials. These were eminent clinicians, experienced and well respected in the field of managing metastatic bone disease with bisphosphonates. It was neither possible nor desirable to censure the views of these independent opinion leaders.

Roche did not necessarily agree with all comments written about its medicines in the press, even when accurate and balanced briefing materials, background data and copies of the summary of product characteristics (SPC) were supplied. There were no consistent inaccuracies as alleged by Novartis.

Roche submitted that although the content of the article was not subject to the Code, it would comment without prejudice on the complaint.

Roche stated that the claim 'Oral treatment for metastatic bone disease' appeared to be a journalistic oversimplification. Roche submitted that its briefing materials made the licensed indication clear.

PANEL RULING

The Panel noted that oral Bondronat was indicated for the prevention of skeletal events in patients with breast cancer and bone metastases. The headline claim at issue 'Oral treatment for metastatic bone disease' gave the impression that Bondronat could be used to treat the metastases *per se* and that was not so. The Panel noted, however, that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself.

The Panel thus examined the material provided to the medical media. The 'Bondronat UK Launch – Pitch Points' document featured nine bullet points: the first introduced Bondronat as part of the management of advanced breast cancer. This was the only bullet point to refer to 'breast cancer', all of the others referred only to 'cancer'. The seventh point described Bondronat as the 'bone saver' which worked by 'effectively slowing the cancer's growth in the bone'. 'Metastatic Bone Disease – Background Information' described the pathophysiology, incidence, risk factors, complications, symptoms and goals of metastatic bone disease management. One goal of metastatic bone disease management read 'ideally, reduce disease progression and improve patient survival'. Although the document concluded by discussing metastatic bone disease and breast cancer this aspect was not mentioned at the beginning of the document, in the heading or such like. Whilst the document did not mention Bondronat it was nonetheless an integral part of the Bondronat press materials. The backgrounder on Bondronat discussed the medicine's mode of action, licensed indications, administration, tolerability and the convenience of oral versus IV presentations. The document explained that 'Bondronat [was] licensed for treatment of tumour-induced hypercalcaemia of malignancy with or without metastases. Prevention of skeletal events in patients with breast cancer and bone metastases'. The section detailing the administration of Bondronat stated 'Bondronat is available as intravenous and oral formulations for the treatment of metastatic bone disease' and that 'For oral use the recommended dose for metastatic bone disease is 50mg once daily'. The document concluded that Bondronat provided 'an important clinical alternative for the treatment of bone metastases'. The medical media release 'Improving quality of life for advanced breast cancer patients with "bone saver"' discussed treatment of metastatic bone disease in breast cancer patients and explained that the 'bone saver' worked by inhibiting the spreading cancer from growing or multiplying in the bone. It therefore reduced bone pain and bone fractures.

The Panel considered that overall the material directed at the medical press, apart from the medical media release 'Improving quality of life for advanced breast cancer patients with "bone saver"', did not make it sufficiently clear that although Bondronat was licensed for metastatic bone disease it was only for metastatic bone disease secondary to breast cancer. It was not licensed to treat metastatic bone disease resulting from any other cause. The Panel considered that the 'Pitch Points' document, the Bondronat backgrounder and the Metastatic Bone Disease – Background Information document were misleading in this regard and inconsistent with the particulars listed in the Bondronat SPC. Breaches of Clauses 7.2 and 3.2 were ruled.

2 Statement 'The oral formulation has equivalent efficacy to the iv drug'

COMPLAINT

Novartis alleged that this claim was misleading as there had been no direct comparisons of the two formulations. Any comparisons made were indirect and inferred. Novartis noted that this claim was currently the subject of an ongoing case; Case AUTH/1572/4/04.

RESPONSE

Roche submitted that this was a key feature of Bondronat and the subject of an appeal in Case AUTH/1572/4/04. In practical medical terms, the efficacy of oral Bondronat was equivalent to that of the IV formulation. This was borne out of the

marketing authorization and no further explanation should be necessary. Roche referred to Clause 7.5 of the Code.

Roche noted that 'equivalent' was defined in three online dictionaries as: 'corresponding or virtually identical especially in effect or function' (Merriam Webster OnLine); 'Essentially equal' (Hyperdictionary); 'Being essentially equal, all things considered … something that performs substantially the same function as another thing in substantially the same way … corresponding or virtually identical in effect of function < drugs that are therapeutically *equivalent*' (Dictionary.com).

Roche noted that the IV Bondronat SPC stated that there was 'a 40% reduction in the risk of SRE [Skeletal Related Events] over placebo (relative risk 0.6, p=0.003)'. For the oral formulation the SPC stated that there was a 38% reduction in the risk of developing an SRE when compared with placebo (relative risk 0.6, p=0.003). The trials used identical inclusion/exclusion criteria. The indication for metastatic bone disease was identical for both formulations. There was no direction as to which to use as both formulations were interchangeable for this indication, all else being equal. Of course, that an individual patient might require one formulation over the other was dictated by their individual clinical circumstances. To state that 40% and 38% were 'equivalent' was correct.

PANEL RULING

The Panel noted that Novartis had not stated a clause of the Code which it alleged had been breached. It had alleged that the statement 'The oral formulation has equivalent efficacy to the iv drug' was misleading as there had been no direct comparisons of the two products and referred to a previous case, Case AUTH/1572/4/04, wherein Novartis had alleged that a closely similar claim was, *inter alia*, misleading and in breach of Clause 7.2 for the same reasons. Case AUTH/1572/4/04 had also involved alleged breaches of Clauses 7.3 and 7.4 in relation to the similar claim. The Panel did not consider that it had allegations before it on these points in the present case; Novartis had described the comparison as misleading: this was adequately covered by Clause 7.2. Roche had responded to the present complaint in relation to the requirements of Clause 7.2 and the Panel thus ruled in relation to the requirements of this clause.

Case AUTH/1572/4/04 concerned an allegation that the claim 'The first 3rd generation bisphosphonate with equivalent oral and IV efficacy' was, *inter alia*, misleading because it gave the impression that there was head-to-head data directly comparing the two; the Panel had upheld the complaint and upon appeal by Roche the Appeal Board had considered that the claim at issue was a strong, unequivocal statement. The claim was referenced to Body *et al* (2003) which had taken the results from three different placebo controlled studies using two different formulations. None of the studies directly compared IV and oral Bondronat. The study authors had concluded, *inter alia*, that their results suggested that both IV and oral Bondronat were equally effective. The Appeal Board noted that such caution was not reflected in the claim at issue. The Appeal Board considered that the claim gave the impression that a direct clinical comparison of IV and oral Bondronat had proven that the two were equally effective which was not so. The Appeal Board thus upheld the Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.4 of the Code.

Turning to the present case, Case AUTH/1599/6/04, the Panel noted that when Roche submitted its response the appeal in Case AUTH/1572/4/04 had not been heard. The Panel considered that the comments and ruling in Case AUTH/1572/4/04 were relevant here. The Panel also considered its general comments upon the press materials at point A1 above were relevant.

The Panel noted that the eighth bullet point in the 'Bondronat UK Launch – Pitch Points' document read 'Bondronat if [sic] the first treatment available as a pill with the same power as its IV formulation'. The Bondronat backgrounder stated '[oral Bondronat] combines intravenous efficacy with oral convenience'. The medical media release 'Improving quality of life for advanced breast cancer patients with "bone saver"' stated that the IV and oral formulations had the same efficacy.

The Panel considered that the 'Bondronat UK Launch – Pitch Points' document, the Bondronat backgrounder and the medical media release gave the impression that a direct clinical comparison of IV and oral Bondronat had proven that the two were equally effective and that was not so. The materials were misleading in this regard. A breach of Clause 7.2 was ruled.

3 Claim 'There are also no adverse renal effects …'

COMPLAINT

Novartis alleged that this absolute statement was untrue since Section 4.8 of the SPC stated that azotaemia (uraemia) had been reported, albeit rarely; the claim was therefore misleading, inconsistent with the terms of the marketing authorization and in breach of Clause 7.2. Since Prescriber was aimed at general practitioners there was also an issue of patient safety since it misled as to the side effect profile of the medicine and was therefore in breach of Clause 2.

RESPONSE

Roche submitted that whilst none of its materials had ever stated that Bondronat had no renal adverse effects, it was common knowledge amongst Bondronat prescribers that it had an excellent renal safety profile. To date, an estimated 500,000 patients had been prescribed Bondronat since its first European launch in 1995. In trials, renal adverse events had been at a level comparable to placebo. For the IV pivotal study 'There was no evidence of renal toxicity associated with ibandronate treatment: the incidence of renal adverse events was low and did not differ between placebo and ibandronate groups' (Body *et al* 2003). For the oral pivotal studies, the incidence of renal adverse events was comparable

between ibandronate (5.2%) and placebo (4.7%), and there were no reports of serious adverse events (renal failure) in the active treatment group (Body *et al* 2004).

Roche submitted that no other bisphosphonate had four year follow-up renal safety data to establish no renal toxicity concerns over long-term therapy (McLachlan *et al* 2003, Rivkin *et al* 2003) and the SPC clearly stated 'Clinical studies have not shown any evidence of deterioration in renal function with long term Bondronat therapy'. There were no published data raising clinical concern about Bondronat's renal safety profile. Even Novartis had admitted that the only cited renal adverse event occurred 'albeit rarely'.

PANEL RULING

The Panel noted its general comments about the press materials in point A1 above. In addition the Panel noted that a section entitled 'What are the side effects with Bondronat' within the Bondronat backgrounder began by discussing the toxicities associated with current bisphosphonates which, it was stated, could limit their clinical benefit. The first of three bullet points read 'infusion of pamidronate and zoledronate can lead to renal toxicity, which, in rare cases, can have severe and life-threatening consequences'. Product labelling and monitoring of patients taking zoledronate was discussed. The safety profile of oral Bondronat was described as 'comparable to placebo'. The Panel considered that the section 'What are the side effects with Bondronat' implied that although renal toxicity had been reported in association with pamidronate and zoledronate none had been reported with Bondronat and that was not so. The medical media release stated that Bondronat had not been associated with increases in renal toxicity or renal adverse events.

The Panel noted that Section 4.8 of the Bondronat tablet SPC listed uraemia as an uncommon adverse event, occurring at a frequency of <1% compared with placebo.

The Panel considered that the Bondronat backgrounder implied that no renal toxicity had been reported with the medicine. The medical media release stated categorically that Bondronat had not been associated with increases in renal adverse events. This was not so. The two documents were misleading in this regard and the Panel ruled a breach of Clause 7.2 of the Code with respect to both. The Panel did not consider that the matter warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

4 Claim '… and the gastrointestinal side-effects of the oral formulation were comparable to placebo'

COMPLAINT

Novartis stated that this statement was untrue and at odds with Section 4.8 of the SPC which had a table of common adverse drug reactions from the pooled phase III trials entitled 'Related Adverse Events Reported Commonly and Greater than Placebo' the table listed dyspepsia, nausea, abdominal pain and oesophagitis, all of which were manifestly gastrointestinal side-effects which were not comparable to placebo. Novartis alleged that the claim was misleading about the side-effect profile of the medicine and potential risks to patient safety in breach of Clauses 7.2 and 2.

RESPONSE

Roche submitted that this appeared to be a journalistic misinterpretation. Gastrointestinal side-effects were compared to placebo and at a very low level. In practice, this tablet was very well tolerated.

PANEL RULING

The Panel considered that its general comments above at points A1 about the media materials were relevant.

The Panel noted that the oral Bondronat SPC listed dyspepsia, nausea, abdominal pain (not otherwise specified) and oesophagitis as events reported commonly (≥ 1% and <10%) and greater than placebo. Also listed were those uncommon (≥ 0.1% and <1%) adverse reactions which had occurred in two studies more frequently with Bondronat 50mg than with placebo. These were abdominal pain, dry mouth, duodenal ulcer haemorrhage, dysphagia and gastritis.

The Panel noted that a section of the Bondronat backgrounder entitled 'What are the side effects with Bondronat' discussed the side effects of other bisphosphonates which had limited their clinical benefit. The third bullet point read 'administration of oral clodronate can cause gastrointestinal disturbances …'. The section concluded with a discussion of Bondronat's side-effect profile, stating, *inter alia*, that the safety profile of Bondronat was comparable to placebo. Overall, the section implied that Bondronat would not cause gastrointestinal disturbance which was not so. The Panel considered that the Bondronat backgrounder was not a fair reflection of the SPC on this point and was thus misleading. A breach of Clause 7.2 was ruled. The Panel did not consider that the matter warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

B DGNews 22 March 2004

1 Heading 'Bondronat (Ibandronate) Appears Effective, Well-Tolerated, Convenient Treatment for Metastatic Bone Disease'

COMPLAINT

Novartis referred to its allegation at point A1 above.

RESPONSE

Roche submitted that whilst the statement 'Bondronat … appears effective, well-tolerated, convenient' was correct, the indication cited appeared to be a journalistic oversimplification. Roche briefing material made the licensed indication quite clear.

PANEL RULING

The Panel considered that its ruling at point A1 above applied here. Breaches of Clauses 3.2 and 7.2 were ruled.

2 Generic name

COMPLAINT

Novartis noted that ibandronate was not the registered generic name for Bondronat.

RESPONSE

Roche stated that it was confused by Novartis' complaint, as it also used 'ibandronate' without qualification in its own promotional materials (Case AUTH/1594/6/04). The registered generic name for Bondronat was ibandronic acid. Ibandronate was a term commonly used by investigators, in publications, and by many users. This issue was clarified in Bondronat materials to avoid any confusion.

PANEL RULING

The Panel noted that Novartis had not stated a clause of the Code which it alleged had been breached nor had it referred either to another part of this complaint or the previous case, Case AUTH/1572/4/04, wherein a clause was clearly stated. The situation was thus different to point A2 above. The complaint did not meet the requirements of Paragraph 5.2 of the Constitution and Procedure. The Panel did not therefore consider this allegation.

3 Claim 'Bondronat was also well tolerated, with patients experiencing adverse events similar to those in the placebo group'

COMPLAINT

Novartis referred to its allegation at points A3 and A4 above.

RESPONSE

Roche made no additional comment on this point.

PANEL RULING

The Panel noted that the DGNews item referred almost exclusively to the publication that day of Body *et al* (2004). In its complaint Novartis had not quoted the whole of the claim which read, in full: 'Bondronat was also well tolerated, with patients experiencing adverse events similar to those in the placebo group with the exception of a small number of patients experiencing mild to moderate gastro-intestinal side effects'. Given the context of the news item it was clear that the claim at issue related only to the findings of one study. The source of the news item was a stated PR agency which the Panel assumed was working on behalf of Roche.

The Panel considered that the claim was a fair and accurate reflection of Body *et al* (2004). Given that the statement clearly related to only one cited study the Panel ruled no breach of Clause 7.2 of the Code. It thus followed that there was no breach of Clause 2 of the Code.

C Article in Future Prescriber, Spring 2004

1 Statement 'The oral drug has advantages over its competitor in that it is a small tablet taken only once daily'

COMPLAINT

Novartis assumed that the competitor was oral clodronate, but it took issue with the fact that being a small tablet, or being taken once daily offered advantages. Novartis noted that Bondronat tablets must be taken after an overnight fast (at least 6 hours) and before the first food or drink of the day and fasting should be continued for at least 30 minutes after taking the tablet. Conversely, Loron capsules might be taken after only an hour's fast. Novartis further noted that the once daily argument was spurious since Loron might also be taken once daily.

Novartis alleged that this statement was misleading and noted that it was currently the subject of the ongoing Case AUTH/1572/4/04.

RESPONSE

Roche submitted that the convenience of oral Bondronat was a key feature of Bondronat and a matter of an appeal (Case AUTH/1572/4/04). Loron could be prescribed once daily but was commonly taken in divided doses (as with other clodronates) due to the large size of the tablets and gastrointestinal intolerance. This was well known and featured in Novartis' own satellite symposium in Davos in March 2004 and in the Major (2004) abstract presented at this international bisphosphonate workshop. It was shown that gastrointestinal toxicity could cause early study discontinuation, with reports of 11-47% of patients reporting upper gastrointestinal adverse events. These data did not include oral Bondronat. In a long-term study of 1,079 patients, gastrointestinal disorders were significantly more common with clodronate (66%) than placebo (56.2%) (Atula *et al* 2003). One might speculate the high placebo level reflected the size of the tablet needed to match the active. Diarrhoea was also significantly more common for clodronate (15.1%) than placebo (6.8%). Complicated regimes and compliance were cited as problems.

PANEL RULING

The Panel noted that Novartis had not stated a clause of the Code which it alleged had been breached. It had described the statement as misleading and referred to Case AUTH/1572/4/04 where a similar claim was alleged to be in breach of Clause 7.2. Roche had responded in relation to the requirements of Clause 7.2 and the Panel thus made its ruling on this basis.

The Panel noted that both parties had referred to the previous case, Case AUTH/1572/4/04, wherein the claim 'So with equivalent efficacy and a small once-daily tablet, compared to IV, Oral Bondronat offers all the convenience of flexibility you could want from today's bisphosphonate therapy' had been at issue. The Panel had noted that there were three oral bisphosphonates indicated for the treatment of patients with breast cancer and bone metastases; Bonefos, Loron and Bondronat. Bonefos and Loron were to be taken in a single dose or two divided doses each day, at least one hour before and one hour after food. Bondronat tablets were to be taken after an overnight fast of at least six hours and at least 30 minutes before the first food or drink of the day. The Panel considered there was thus less flexibility with regard to the time of day that a patient could take Bondronat compared with the other oral bisphosphonates. If a patient forgot to take Bondronat first thing in the morning, before breakfast, it would be difficult to take it at any other time of day given the need to fast for at least six hours beforehand and 30 minutes after. Patients who forgot to take either Bonefos or Loron could take it later in the day as long as there was a period of at least two hours where they did not eat; to take Bondronat later in the day required a period of at least six and a half hours of no food. The Panel noted Roche's submission about the small tablet size but noted that there was no data to show whether patients found these more or less convenient than other bisphosphonate tablets. The Panel thus considered that in the context of 'today's bisphosphonate therapy' oral Bondronat was less convenient and flexible in terms of timing of dosage than other oral bisphosphonates. The Panel thus ruled breaches of Clauses 7.2, 7.3, 7.4 and 7.10 of the Code. On appeal by Roche the Appeal Board considered, *inter alia*, that the claim was more than a comparison between IV and oral. The reference to 'today's bisphosphonate therapy' turned the claim into a comparison of oral Bondronat with all other bisphosphonates. The Appeal Board thus considered that by stating oral Bondronat offered **all** (emphasis added) the convenience and flexibility a prescriber could want … the claim was misleading, not capable of substantiation and exaggerated as alleged. The Appeal Board had upheld the Panel's rulings of breaches of the Code.

Turning to the case now before it, Case AUTH/1599/6/04, the Panel noted that the article in Future Prescriber referred to clodronate and zoledronic; both were competitors to Bondronat. Zoledronic acid (Zometa) was only available as an IV formulation and so the Panel assumed that in the statement at issue the competitor referred to was clodronate.

The Panel noted that both the medical media release and the Bondronat backgrounder stated that Bondronat was to be taken once daily. The Bondronat backgrounder additionally noted that Bondronat was a small tablet. Neither document referred to the size of clodronate tablets nor to their frequency of administration. None of the materials compared the tablet size or frequency of administration of Bondronat with clodronate; no breach of Clause 7.2 was ruled.

2 Claim 'The manufacturers are investigating a potential inhibitory effect on bone tumours …. There are also trials underway … in [metastatic bone disease] associated with other cancers, such as lung, prostate and myeloma'

COMPLAINT

Novartis noted that the Code allowed advance notification of new indications to budget holders for planning purposes. However, Novartis alleged that the readership of Future Prescriber could not be assumed only to fulfil the criteria of budget holders; many would be prescribers. Thus to give information to journalists about unlicensed indications constituted a breach of Clause 3.2.

RESPONSE

Roche submitted that its briefing materials did not include information about further areas of research. This speculation might have come from an independent clinician.

PANEL RULING

The Panel noted that none of the press materials provided by Roche referred to ongoing or future trials with Bondronat in unlicensed indications. No breach of Clause 3.2 was ruled.

D E-mims April 2004

Claim 'For many patients with metastatic bone disease treatment with intravenous bisphosphonates is complicated by infusion-related adverse events and the potential for renal toxicity. Therefore, an effective oral formulation offers an important alternative'

COMPLAINT

Novartis alleged that as in point A3 above this implied that oral Bondronat did not have the potential for renal toxicity.

RESPONSE

Roche did not comment further on this point.

PANEL RULING

The Panel considered that its comments and rulings at point A3 above were relevant. A breach of Clause 7.2 was ruled. No breach of Clause 2 was ruled.

E Article entitled 'A Pain-Free Future'. The Times, Friday 19 March 2004

1 Claims 'There is now a drug that could help such women to lead relatively normal lives' and 'One of the other benefits of Bondronat is that it is the first drug in its class – the so-called bisphosphonates – that can be taken orally without the need for regular intravenous injections or infusions in hospital'

COMPLAINT

Novartis alleged that these statements were misleading since they implied that no such medicine was available previously which was clearly inaccurate, since several bisphosphonates, both oral and IV were already available for treatment of breast cancer metastatic to bone. Additionally, Roche's own product, Loron, had been available orally for some time. This should have been made clear in any briefing, in particular to the lay press. These statements were misleading and in breach of Clause 7.2.

RESPONSE

Roche submitted that a general comment could be made here about the statements that appeared in the lay press. Roche stated that its briefing materials were clear but the lay press had taken a degree of latitude, for which Roche could not be held responsible.

PANEL RULING

The Panel noted its general comments about press materials at point A1 above.

The Panel noted that the consumer media release stated that Bondronat was 'the first and only treatment of its kind to be available in IV and oral formulations, with the same efficacy …'. The Panel considered that it was unclear as to what the first referred to ie 'treatment of its kind', 'available in IV and oral' or 'with the same efficacy'. The Panel considered that the consumer media release was ambiguous and misleading as to the 'first' that Bondronat represented. A breach of Clause 7.2 was ruled.

2 Claims '… Bondronat, which was originally developed as a treatment for osteoporosis …' and 'As a drug for osteoporosis, …'

COMPLAINT

Novartis alleged that as Bondronat was not licensed for osteoporosis these statements were in breach of Clause 3.2 and 20.4 since the introduction of a new medicine must not be made known to the general public until the medical and pharmaceutical professions had been informed of its availability, which was clearly not the case.

RESPONSE

Roche referred to its response at point E1 above.

PANEL RULING

The Panel noted that none of the press materials provided referred to Bondronat and osteoporosis. The Panel thus ruled no breach of Clauses 3.2 and 20.4 of the Code.

3 Claim '… a frontline treatment to prevent cancer spreading beyond the breast'

COMPLAINT

Novartis referred to its allegation at point E2 above.

RESPONSE

Roche referred to its response at point E1 above.

PANEL RULING

The Panel noted that the statement in The Times article read, 'Bondronat … could also have a more important impact as a frontline treatment to prevent cancer spreading beyond the breast'. The claim thus referred to a possible future use of Bondronat. The Panel noted its comments at point C2 above. The Panel ruled no breach of Clauses 3.2 and 20.4 of the Code.

4 Claim '(This does not affect the drug's use for bone pain, for which it is licensed)'

COMPLAINT

Novartis alleged that clearly the journalist was aware of the licensed indication for this product.

RESPONSE

Roche referred to its response at point E1 above.

PANEL RULING

The Panel noted that Novartis had not stated a clause of the Code which it alleged had been breached. It appeared that in fact there was no complaint about the statement. The situation was different to point A2 above. The complaint did not meet the requirements of Paragraph 5.2 of the Constitution and Procedure. The Panel did not therefore consider this matter.

5 Claim 'If secondary cancer could be prevented, then many patients could stay disease-free'

COMPLAINT

Novartis alleged that since Bondronat was not licensed for this indication, the claim raised unfounded hopes and was in breach of Clause 20.2.

RESPONSE

Roche referred to its comments at point E1 above.

PANEL RULING

The Panel noted that the claim at issue was a quotation from a medical oncologist. The quotation was not included in any of the Bondronat press materials provided by Roche and nor was there any reference to the particular medical oncologist. The Panel ruled no breach of Clause 20.2.

F Article entitled 'New breast cancer drug'. Bella, 11 May 2004

1 Claim 'New breast cancer drug'

COMPLAINT

Novartis alleged that as Bondronat was not licensed for breast cancer, this heading was in breach of Clause 3.2.

RESPONSE

Roche referred to its comments at point E1 above.

PANEL RULING

The Panel did not consider that any of the press materials provided by Roche gave the impression that Bondronat was licensed to treat breast cancer. No breach of Clause 3.2 was ruled.

2 Claim 'Ibandronic acid (brand name Bondronat) is the first and only treatment of its kind proven to offer patients up to two years relief from the often severe and disabling pain …'

COMPLAINT

Novartis referred to point E1 above.

RESPONSE

Roche referred to its comments at point E1 above.

PANEL RULING

The Panel noted that the claims at issue at point E1 above were general in nature whereas the claim now at issue was very clear as to the feature being discussed ie two year pain relief data. The Panel noted that the article was closely similar to a claim in the consumer media press release. However, the Panel noted that the allegation in point E1 was that claims were misleading and in breach of Clause 7.2 of the Code. Novartis had not provided any data to show that Bondronat was not the first bisphosphonate to offer patients up to two years of pain relief. Roche had not provided any data or response. The Panel decided that in the light of the complaint and the response it had no choice other than to rule no breach of Clause 7.2.

Complaint received **23 June 2004**

Case completed **17 September 2004**

CASE AUTH/1600/6/04

DENFLEET PHARMA v NOVARTIS

Clozaril booklets

Denfleet Pharma complained about two booklets issued by Novartis which compared Novartis' product Clozaril (clozapine) with generic clozapine. One was entitled 'Generic clozapine – why take the risk in at risk patients?' and the other 'WHO will pay the price for generic clozapine?'. Novartis stated that the aim was to outline issues that needed to be considered when assessing alternative suppliers of clozapine and to provide evidence emerging from the US regarding the use of generic clozapine. Denfleet marketed Denzapine (clozapine), a branded generic. Clozapine was an atypical antipsychotic medicine.

The claim '88% of patients said they would prefer to stay on Clozaril rather than change to another drug' appeared in the booklet 'Generic clozapine – why take the risk in at risk patients?'. Denfleet stated that since the booklet related to the switching of patients from Clozaril to generic clozapine, this claim was misleading; it inferred that patients would rather stay on Clozaril than another medicine, including generic clozapine. The cited paper (Taylor *et al* 2000) actually referred to patients' preference for clozapine rather than the previous antipsychotic they were taking.

The Panel noted that Taylor *et al* asked patients, most of whom had been taking clozapine for two years or more, to compare clozapine with their previous treatment which included oral typical medicines, depot typical and oral atypical; the majority (62.1%) of respondents rated clozapine as being better. The Panel considered the claim was misleading and had not been substantiated as it was not sufficiently clear that the comparison was with medicines other than clozapine. Context was a contributory factor as the purpose of the booklet was to compare generic clozapine with Clozaril. Breaches of the Code were ruled.

The claim 'Generally, bioequivalent drug products are considered to be therapeutically equivalent …' appeared on a page headed 'What does "bioequivalent" actually mean?'. The claim was referenced to UK regulatory guidance on bioavailability and bioequivalence and a Food and Drug Administration (FDA) letter to health professionals regarding the therapeutic equivalence of generic drugs.

Denfleet alleged that the use of the word 'generally' was misleading as it implied some level of variability. As far as the FDA was concerned, a medicine was either considered bioequivalent and therapeutically equivalent, or not. The FDA's letter regarding therapeutic equivalence of generic medicines, stated that 'For both brand-name and generic medicines, FDA works with pharmaceutical companies to assure that all drugs marketed in the US meet specifications for identity, strength, quality, purity and potency. In approving a generic drug product, FDA requires many rigorous tests and procedures to assure that the generic drug is interchangeable with the brand-name drug under all approved indications'. The FDA published a list of brand name medicines and therapeutically equivalent generic products. Several formulations of generic clozapine were listed as therapeutically equivalent. Therefore, the use of 'generally' in the claim was misleading.

The Panel considered that there might be occasions when bioequivalent medicines were not considered to be therapeutically equivalent, for example when site of action was a key factor or there were differences in absorption rate. The UK regulatory guidance stated 'However, in some cases where similar extent of absorption but different rates of absorption are observed the products can still be judged therapeutically equivalent if those differences are not of therapeutic relevance. A clinical study to prove that the differences in absorption rate are not therapeutically relevant will probably be necessary'. The Panel did not consider that the claim was misleading as alleged and thus ruled no breach of the Code.

Denfleet stated that a page headed 'What do the studies show?' wrongly implied that the US was the only country in which generic clozapine was available, when in fact it was also available throughout Europe, South Africa and Australasia. Denzapine, one of the two branded generic clozapines available in the UK, had not sought marketing authorization approval in the US until this time. No reference was made to this in the booklet and therefore any problems due to the use of generic clozapine in the US could not apply to Denzapine. Denfleet alleged that to disseminate data in this blanket manner to UK psychiatrists was misleading.

Denfleet stated that two of the three references (Kluznik *et al* 2001; Mofsen and Balter 2001; Price 2001) which discussed relapse were presented at a seminar sponsored by an unrestricted educational grant from the Novartis Pharmaceuticals Corporation. This did not represent a balanced view of the information currently available. The cases of relapse presented by Price were raised during a symposium discussion; no details were presented or published in a peer reviewed journal. The use of this type of reference was misleading. The booklet did not include references to clinical studies, reported in peer-reviewed journals, where patients had been successfully switched to generic clozapine without reported relapse, eg Sajbel *et al* (2001), Stoner *et al* (2003) and Makela *et al* (2003). A quotation from Kelleher (2001) was referenced incorrectly.

The Panel considered that the page implied that generic clozapine was only available in the US. This was not so. Breaches of the Code were ruled. The Panel did not accept that it was necessarily misleading to present data about the US use of generic clozapine to UK physicians when Denfleet's clozapine, Denzapine, was not available in the US. No breach of the Code was ruled in this regard.

The Panel did not accept it was necessarily misleading to use references presented at Novartis'

sponsored seminar. No breach of the Code was ruled on this narrow point. However the Panel noted Denfleet's submission that there were studies showing switching without relapse. None had been provided to the Authority by either party. In the Panel's view, given the allegation, Novartis had not demonstrated that the data in the booklet represented the balance of the evidence. The Panel thus ruled breaches of the Code.

The Panel noted that the reference to Kelleher (2001) should have stated Kelleher (2002). A breach of the Code was ruled.

Denfleet alleged that the question 'Without the support network associated with the CPMS (Clozaril Patient Monitoring Service), how many patients will relapse?' which appeared in the section headed 'Relapse', implied that without the support of the CPMS patients might relapse more frequently. This was misleading; relapse could be caused by many factors and could occur in patients where full adherence to medication was confirmed.

The Panel considered that the question at issue implied that the support network associated with the CPMS prevented relapse. This was not so. The question was misleading and its implication was not capable of substantiation. Breaches of the Code were ruled.

The claim 'nearly 10% decrease in serum clozapine concentration' appeared as part of a description of the outcome of Kluznik *et al* which looked at the clinical effects of a randomised switch of patients from Clozaril to generic clozapine. The claim appeared next to the claim 'nearly 20mg/day increase in dose p=0.027'. Denfleet stated that Kluznik *et al* showed that there was no statistically significant difference between the mean serum clozapine levels of patients receiving Clozaril and a generic clozapine and, therefore, no meaningful conclusion could be drawn from the results. The claim was misleading and inaccurate.

The Panel noted that Kluznik *et al* reported statistically significant differences between Clozaril and generic clozapine with regard to daily dose; 610.17mg vs 629.5mg, p=0.027. Serum norclozapine levels were lower for generic clozapine than Clozaril (p=0.01). The difference in serum clozapine levels although lower for generic clozapine was not statistically significant (p=0.085). The claim at issue was not supported by a statistically significant difference. The Panel considered that the claim was misleading and not capable of substantiation. Breaches of the Code were ruled.

Details of relapse in patients in a study by Mofsen and Balter were described. Denfleet noted that the study authors had stated that it was not possible to conduct a detailed analysis of all the variables in this retrospective assessment. In Denfleet's view this concurred with its opinion that Mofsen and Balter was based on purely anecdotal evidence, and, therefore, no meaningful comparisons could be drawn.

The Panel noted that Mofsen and Balter concluded that the findings suggested that brand-name clozapine and the generic formulation might display important clinical differences and a comparable therapeutic response might not be achievable despite adequate monitoring. Large controlled prospective trials were needed to clarify the potential for treatment failure with the use of generic clozapine. The Panel considered that the case reports had not been presented in sufficient context. The limitations of the data as identified by Denfleet were not mentioned. The Panel considered that this was misleading and hence not capable of substantiation. Breaches of the Code were ruled.

In relation to the booklet, 'WHO will pay the price for generic clozapine', Denfleet stated that on 26 April it had complained to Novartis about this booklet which was almost identical to that referred to above. On 30 April, Novartis replied that its booklet had been withdrawn, revised and reissued to the sales force. Although Denfleet did not entirely accept Novartis' attitude, it nonetheless considered the matter dealt with. However, Denfleet noted that the booklet was given to medical staff at a hospital during the week of 7 June by a Novartis sales representative. The hospital pharmacy department was horrified that this had occurred and immediately forwarded a copy to Denfleet. It also noted with concern that the Novartis representative was on the wards without having signed the register at the pharmacy department in contravention of local procedure. Denfleet stated that it appeared that the booklet was also still being used in other areas of the country.

The Panel noted that the parties' accounts of events differed. Denfleet had received a copy of the booklet 'WHO will pay the price for generic clozapine?' which had allegedly been recently given to hospital pharmacy staff by the Novartis representative. No evidence had been provided by the complainant to show that recently the hospital had a policy for visiting representatives nor that if such a policy existed that it had not been followed. On the basis of the information before it the Panel decided that it had no option other than to rule no breach of the Code.

Denfleet referred to the section entitled 'What do the studies show? on a page headed 'What does "bioequivalent" actually mean ?'. This was followed by 'Evidence from several pharmacokinetic studies looking at bioequivalence have shown conflicting results'. Denfleet also alleged that the section 'What do the studies show?' contained misleading and inaccurate information. Pharmacokinetics was the study of the absorption, distribution, metabolism and excretion of medicines yet the studies appearing on this page (Kluznik *et al*, Mofsen and Balter and Price) did not examine the pharmacokinetic parameters required to determine bioequivalence. Denfleet alleged that the statement 'Evidence from several pharmacokinetic studies …' was inaccurate, misleading and not supported by the studies presented.

The Panel noted that the studies cited were not pharmacokinetic studies as such. Mofsen and Balter presented seven case studies of patients who experienced a relapse of psychotic symptoms when

they were switched from branded clozapine to a generic formulation. Kluznik *et al* studied the clinical effects of a randomised switch of patients from Clozaril to generic clozapine. Serum concentrations were measured. Price was taken from a discussion at a symposium which described a switch of patients from Clozaril to generic clozapine. The claim 'Evidence from several pharmacokinetic studies looking at bioequivalence have shown conflicting results' followed by a description of the three studies was thus misleading and not capable of substantiation. Breaches of the Code were ruled.

Beneath the heading 'How will the Clozaril Patient Monitoring Service (CPMS) support you?' and beneath the subheading 'The comprehensive CPMS package' appeared the claim '30% of the cost of plasma drug concentration monitoring (required while titrating dose) is covered by the CPMS' which Denfleet alleged was misleading and inaccurate.

Denfleet stated that clozapine dosage was normally adjusted according to clinical response and adverse effect profile. The measurement of plasma clozapine concentrations was useful in assessing compliance, optimising therapy and minimising toxicity. Plasma drug level monitoring was not required whilst titrating the dose.

The Panel noted that the Clozaril summary of product characteristics (SPC) stated that white blood cell (WBC) count and differential blood counts must be performed within 10 days prior to initiating Clozaril treatment to ensure that only patients with WBC counts and absolute neutrophil count (ANC) within certain given parameters received the medicine. After the start of treatment the WBC count and ANC must be monitored weekly for the first 18 weeks of therapy and at least every four weeks thereafter throughout treatment. The use of Clozaril was restricted to patients, physicians and nominated pharmacists registered with the CPMS.

The only detailed information about monitoring was in the claim at issue which implied that monitoring was only required when titrating the dose and only plasma drug concentration monitoring was necessary. This was not so. The SPC required WBC and ANC monitoring at different frequencies depending on how long the patient had been taking Clozaril. The maximum period was at least every four weeks.

The Panel was very concerned that the statement in the booklet gave a very different impression of the monitoring requirements compared to those in the SPC. The statement at issue might compromise patient safety. The Panel considered the statement was misleading and not capable of substantiation as alleged. Breaches of the Code were ruled.

Denfleet Pharma Ltd complained about two booklets issued by Novartis Pharmaceuticals UK Ltd which compared Novartis' product Clozaril (clozapine) with generic clozapine. One was entitled 'Generic clozapine – why take the risk in at risk patients?' and the other 'WHO will pay the price for generic clozapine?'. Both bore the reference CLZ/03/78.

The booklets were distributed by representatives to hospital pharmacists and hospital psychiatrists from the end of January 2004 until withdrawal on 30 April 2004. Novartis stated that the aim was to outline issues that needed to be considered when assessing alternative suppliers of clozapine and to provide evidence emerging from the US regarding the use of generic clozapine.

Denfleet Pharma marketed Denzapine (clozapine), a branded generic. Clozapine was an atypical antipsychotic medicine.

Denfleet alleged breaches of UK law as well as of Clauses 7.2, 7.4, 14.4, 15.2 and 15.4 of the Code. The Panel only considered the alleged breaches of the Code. In addition to these clauses Denfleet cited some specific clauses with some of the allegations below. In such circumstances the Panel also considered the most relevant clauses from the general allegations.

A Booklet entitled 'Generic clozapine – why take the risk in at risk patients?'

1 Claim '88% of patients said they would prefer to stay on Clozaril rather than change to another drug'

The claim appeared on page 7 as part of a two page spread (pages 6 and 7) headed 'How will the Clozaril Patient Monitoring Service (CPMS) support you?' and was referenced to Taylor *et al* (2000).

COMPLAINT

Denfleet stated that since the booklet related to the switching of patients from Clozaril to generic clozapine, this quotation was misleading; it inferred that patients would rather stay on Clozaril than another medicine, including generic clozapine. The referenced paper actually referred to the patients' preference for clozapine rather than the previous antipsychotic they were taking. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Novartis stated that the claim was at the end of a section highlighting the proven benefits of Clozaril and the high standard of professional service offered by the CPMS. The claim was taken from Taylor *et al* 2000 which evaluated patient perceptions of Clozaril treatment and was solely intended to reinforce the positive perception patients had of Clozaril compared to previous therapy despite some disadvantages of treatment such as mandatory monitoring and side-effects. It was clear that the claim referred to another molecule and not a generic version of Clozaril. Novartis did not accept there had been a breach of Clause 7.2 of the Code. However, to enhance clarity, the claim had now been withdrawn from future materials.

PANEL RULING

The Panel noted that the claim at issue was not a quotation as stated by Denfleet.

The Panel noted that Taylor *et al* surveyed perceptions of patients most of whom had been taking clozapine for two years or more. Patients were asked to compare clozapine with their previous treatment which included oral typical medicines, depot typical and oral atypical with the overwhelming majority of respondents rating clozapine as being better (62.1%).

The Panel considered the claim was misleading and had not been substantiated as it was not sufficiently clear that the comparison was with medicines other than clozapine. Context was a contributory factor as the purpose of the booklet was to compare generic clozapine with Clozaril. Breaches of Clauses 7.2 and 7.4 of the Code were ruled.

2 Claim 'Generally, bioequivalent drug products are considered to be therapeutically equivalent …'

This claim appeared on page 11 headed 'What does "bioequivalent" actually mean?'. The claim was referenced to a Committee for Proprietary Medicinal Products (CPMP) Note for Guidance on Bioavailability and Bioequivalence (2001) and a Food and Drug Administration (FDA) letter to health professionals sent in 1998 regarding the therapeutic equivalence of generic drugs.

COMPLAINT

Denfleet alleged that the use of the word 'generally' was misleading as it implied some level of variability. As far as the FDA was concerned, a medicine was either considered bioequivalent and therapeutically equivalent, or not. There was no grey area as far as the FDA was concerned. To imply a degree of variability was misleading. The FDA's letter regarding therapeutic equivalence of generic medicines, sent to health professionals in January 1998, stated that 'For both brand-name and generic medicines, FDA works with pharmaceutical companies to assure that all drugs marketed in the US meet specifications for identity, strength, quality, purity and potency. In approving a generic drug product, FDA requires many rigorous tests and procedures to assure that the generic drug is interchangeable with the brand-name drug under all approved indications'.

The FDA identified brand name drug products and therapeutically equivalent generic products in its publication, 'Approved Drug Products with Therapeutic Equivalence Evaluations' or 'Orange Book'. Several formulations of generic clozapine were listed in the Orange Book as therapeutically equivalent. Therefore, the use of 'generally' in the claim was misleading.

RESPONSE

Novartis stated that the claim at issue, as well as being referenced to the FDA letter and to the CPMP guidance on bioequivalence, was followed by a quotation from Ereshefsky and Glazer (2001) in which the authors stated that FDA approval of bioequivalence was not a guarantee of therapeutic equivalence, rather a statement of probability that most patients would experience no clinically meaningful differences.

Novartis stated that the claim inferred that whilst bioequivalent medicines were classified as being therapeutically equivalent, there was debate in the published literature as to the exact implication of this classification in clinical practice. Additionally, the CPMP Guidance point 2.6 Therapeutic equivalence, stated '*In practice*, demonstration of bioequivalence is generally the most appropriate method of substantiating therapeutic equivalence…'. Novartis did not consider that the claim was misleading; however, for enhanced clarification, the word 'generally' had now been removed from future materials.

PANEL RULING

The Panel considered that there might be occasions when bioequivalent medicines were not considered to be therapeutically equivalent; for example when site of action was a key factor or there were differences in absorption rate.

The Panel noted that the CPMP Note for Guidance also stated in Paragraph 2.6 'However, in some cases where similar extent of absorption but different rates of absorption are observed the products can still be judged therapeutically equivalent if those differences are not of therapeutic relevance. A clinical study to prove that the differences in absorption rate are not therapeutically relevant will probably be necessary'.

The Panel did not consider that the claim was misleading as alleged and thus ruled no breach of Clauses 7.2 and 7.4 of the Code.

3 Page 12 headed 'What do the studies show?'

Page 12 stated that 'Evidence from several pharmacokinetic studies looking at bioequivalence have shown conflicting results' and 'In the USA where generics are available, reports of relapse have emerged'. This was followed by details of three studies looking at relapse, Kluznik *et al* (2001), Mofsen and Balter (2001) and Price (2001).

COMPLAINT

Denfleet stated that page 12 implied that the US was the only country in which generic clozapine was available. This was incorrect. Generic clozapine was also available throughout Europe, South Africa and Australasia.

Denzapine, one of the two branded generic clozapines available in the UK, had not sought marketing authorization approval in the US until this time. No reference was made to this anywhere in the booklet and therefore any reference to problems having arisen with the use of generic clozapine in the US could not possibly apply to Denzapine. Denfleet alleged that to disseminate data in this blanket manner to UK psychiatrists was misleading in breach of the Code.

Denfleet stated that two of the three references which discussed relapse were presented at a seminar sponsored by an unrestricted educational grant from

the Novartis Pharmaceuticals Corporation. This did not represent a balanced view of the information currently available. The cases of relapse presented by Price were raised during a symposium discussion. No details of the cases were presented or published in a peer reviewed journal. The use of this type of reference was misleading.

Denfleet stated that the booklet did not include references to clinical studies, reported in peer-reviewed journals, where patients had been successfully switched to generic clozapine without reported relapse, eg Sajbel *et al* (2001), Stoner *et al* (2003) and Makela *et al* (2003).

Denfleet alleged that the quotation from Kelleher (2001) 'Until more data are available, clinicians should weigh the potential for additional risk with generic clozapine against the moderate cost savings that can be realised with generic products' on page 12 was referenced incorrectly.

RESPONSE

Novartis submitted that the statement 'In the USA where generics are available, reports of relapse have emerged' was not misleading. It did not imply that the US was the only country where generics were available, merely that generics were available in the US and evidence relating to their use had emerged. However, for enhanced clarification, for future materials the sentence had been amended as follows: 'In the USA, one of the countries where generics are available …'.

Novartis submitted that it had not stated that Denzapine was not available in the US because the booklet referred to issues with generic clozapine in general and not to any specific brands. Novartis stated that it was not required to refer to any of the branded generics available in the UK specifically by name and there was no breach of the Code.

With regard to Denfleet's concerns relating to the use of references presented at a seminar sponsored by an unrestricted educational grant from Novartis and the reference in the booklets to case histories presented during a symposium discussion, Novartis pointed out that Clause 7.4 stated that 'Any information, claim or comparison must be capable of substantiation'. As such, inclusion of published anecdotal evidence or case histories or evidence obtained from sponsored educational seminars was permitted. Therefore, Novartis submitted that no breach had occurred.

With regard to Denfleet's concerns regarding the lack of references to clinical studies where patients had been successfully switched and that the publications described were not pharmacokinetic studies, Novartis pointed out that the first sentence in the booklet relating to the available evidence stated 'Evidence from several pharmacokinetic studies looking at bioequivalence have shown conflicting results'. This was a stand-alone sentence which clearly stated the available evidence was conflicting. It was capable of substantiation. Hence, Novartis submitted that the statement was not misleading and that no breach had occurred. However, for improved clarification, in future materials the text had been expanded to state that the evidence from studies evaluating pharmacokinetic parameters and the switch of patients from branded to generic clozapine was conflicting. Specific references to studies had also been included.

Novartis stated that Kelleher publication was incorrectly cited as 2001 instead of 2002 and this typographical error had subsequently been corrected.

PANEL RULING

The Panel considered that the page implied that generic clozapine was only available in the USA. This was not so. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel did not accept that it was necessarily misleading to present data about the USA use of generic clozapine to UK physicians when Denfleet's clozapine, Denzapine, was not available in the USA. No breach of Clauses 7.2 and 7.4 of the Code was ruled.

The Panel did not accept it was necessarily misleading to use references presented at Novartis' sponsored seminar. No breach of Clauses 7.2 and 7.4 was ruled on this narrow point. However the Panel noted Denfleet's submission that there were studies showing switching without relapse. None had been provided to the Authority by either party. In the Panel's view given the allegation Novartis had not demonstrated that the data in the booklet represented the balance of the evidence. The Panel thus ruled breaches of Clauses 7.2 and 7.4 of the Code.

The Panel noted that the reference to Kelleher (2001) was incorrect, it should have stated Kelleher (2002). A breach of Clause 7.2 was ruled.

4 Question 'Without the support network associated with the CPMS, how many patients will relapse?'

Page 14 listed features which might contribute to the cost of switching. The question at issue appeared in the section headed 'Relapse'.

COMPLAINT

Denfleet alleged that the question implied that without the support of the CPMS patients might relapse more frequently. This was misleading; relapse could be caused by many different factors and could occur in patients where full adherence to medication was confirmed.

RESPONSE

Novartis submitted that the statement referred to the high standard of support health professionals received from Novartis and the CPMS in the management of this complex and frequently difficult to manage group of patients. For example in the management of adverse events and the avoidance of unnecessary treatment discontinuations. However, based on the decision to shorten the booklet page 14 had been removed from future materials.

PANEL RULING

The Panel considered that the question at issue implied that the support network associated with the CPMS prevented relapse. This was not so. The question was misleading and its implication was not capable of substantiation. The Panel ruled breaches of Clauses 7.2 and 7.4 of the Code.

5 Claim 'nearly 10% decrease in serum clozapine concentration'

The claim appeared on page 19 as part of a description of the outcome of a study by Kluznik *et al* which looked at the clinical effects of a randomised switch of patients from Clozaril to generic clozapine. The claim appeared next to the claim 'nearly 20mg/day increase in dose p=0.027'.

COMPLAINT

Denfleet stated that the results of Kluznik *et al* showed that there was no statistically significant difference between the mean serum clozapine levels of patients receiving Clozaril and a generic clozapine and, therefore, no meaningful conclusion could be drawn from the results. The claim was misleading and inaccurate, in breach of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Novartis stated that the claim was included as part of a diagrammatic illustration to support the statement: 'There was a significant increase in the dose of medication prescribed yet a decrease in serum clozapine concentrations following the switch from branded to generic clozapine'. This was one of the findings in Kluznik *et al* in conjunction with reports of patient relapse which led the authors to conclude that generic and branded clozapine might not be bioequivalent. Novartis disagreed with the complainant's view that no meaningful comparisons could be drawn from the results; however, the detailed description of the study had been removed from future materials based on the decision to shorten the documents.

PANEL RULING

The Panel noted that Kluznik *et al* reported statistically significant differences between Clozaril and generic clozapine with regard to dose; patients on a generic form of Clozaril took a mean dose of 629.5mg per day, patients on Clozaril took 610.17mg per day (p=0.027) and serum norclozapine levels were lower for generic clozapine than Clozaril (p=0.01). The difference in serum clozapine levels although lower for generic clozapine was not statistically significant (p=0.085). The claim at issue was not supported by a statistically significant difference. The Panel considered that the claim was misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled.

6 'Case reports of relapse'

Pages 20, 21 and 22 described details of relapse in patients in a study by Mofsen and Balter.

COMPLAINT

Denfleet noted that the background to Mofsen and Balter stated that it was not possible to conduct a detailed analysis of all the variables in this retrospective assessment. In Denfleet's view this concurred with its opinion that Mofsen and Balter was based on purely anecdotal evidence, and, therefore, no meaningful comparisons could be drawn.

RESPONSE

Novartis stated that the background to Mofsen and Balter referred to the analysis of all variables. The authors continued in the next sentence to state that 'However, factors other than the switch to a generic formulation of clozapine that could have caused or contributed to patients' deterioration (eg concomitant medications) were actively sought'. Furthermore, the authors, in support of their conclusions noted the strong temporal link between relapse and the switch to generic clozapine. The authors therefore based their causality assessments on the evaluation of possible confounders and the temporal association with the onset of relapse, as was standard practice in the evaluation of adverse events. Novartis disagreed with Denfleet's view that no meaningful comparisons could be drawn from this data. Use of case histories and anecdotal evidence was permitted under the Code. However, for enhanced clarification, an introductory paragraph documenting the authors' background information had been added to future materials.

PANEL RULING

The Panel noted that Mofsen and Balter concluded that the findings suggested that brand-name clozapine and the generic formulation might display important clinical differences and a comparable therapeutic response might not be achievable despite adequate monitoring. Large controlled prospective trials were needed to clarify the potential for treatment failure with the use of generic clozapine.

The Panel considered that the case reports had not been presented in sufficient context. The limitations of the data as identified by Denfleet were not mentioned. The Panel considered that this was misleading and hence not capable of substantiation. Breaches of Clauses 7.2 and 7.4 of the Code were ruled.

B Booklet entitled 'WHO will pay the price for generic clozapine?'

1 Alleged distribution by a representative

COMPLAINT

Denfleet stated that on 26 April, it had complained to Novartis about the above booklet which was almost identical to that referred to in point A above, containing all of the errors noted above plus several more. Novartis responded on 30 April, stating that its booklet had been withdrawn, revised and reissued to the sales force.

Denfleet stated that whilst not entirely accepting Novartis' attitude towards the errors and the fact that it had no intention of communicating the inaccuracies to health professionals who had received the original publication, Denfleet considered the matter had been dealt with. However, Denfleet noted that Novartis was still using the booklet and had made no attempt to correct any of the errors.

Specifically the booklet was given to medical staff at a hospital during the week of 7 June by a Novartis sales representative. The pharmacy department at the hospital was horrified that this had occurred and immediately forwarded a copy to Denfleet. It was also horrified to note that the representative was present on the wards without having signed the register at the pharmacy department, thus contravening local hospital procedure. Denfleet stated that it appeared that the booklet was also still being used in other areas of the country.

RESPONSE

Novartis stated that it had responded promptly and fully to the same issues raised by Denfleet in April; furthermore, Denfleet received written reassurance from Novartis, dated 30 April, that the materials in question had been withdrawn from use. A statement from the representative confirmed that he did not distribute the materials at the hospital as alleged.

Novartis regretted that, given the full cooperation extended by it in responding to this matter, Denfleet was unable to contain this issue at an inter-company level but had taken the matter not only to the Authority but also to the Medicines and Healthcare products Regulatory Agency (MHRA).

Novartis stated that it took its responsibility to act in a highly professional manner and in accordance with the Code extremely seriously. As noted in its letter of 30 April it confirmed to Denfleet that during its spring sales conference, 26-30 April, the sales force had been notified that the decision had been made to withdraw the materials as new materials were in production. On return to the company office a further email confirming this withdrawal was sent to the field force.

Novartis was therefore concerned to hear that a member of its field-force had allegedly given out a copy of the withdrawn material to medical staff at a hospital during the week of 7 June, and that copies of the materials were still in use in other parts of the country in breach of company procedures. Novartis stated that the representative attended the psychiatric intensive care unit at the hospital on 10 June at the invitation of the lead nurse; email correspondence between the two regarding the visit was provided. The representative confirmed that he did not distribute copies of the withdrawn brochure during this visit. Other recent dates that he visited the hospital were 21 May and 2 June. On 21 May he and the Clozaril national strategic account manager visited the principal pharmacist. Again, the representative stated that he did not distribute any of the withdrawn materials. This fact could be verified by the Clozaril national strategic account manager. The representative made a follow-up visit on his own to the principal pharmacist on 2 June, during which she asked for a copy of one of the booklets but was told that these were no longer available.

With reference to the allegation relating to the representative being present on the wards without permission, therefore breaching local hospital policy, he stated that neither he nor any colleagues who had worked in that region for up to 15 years were aware of any policies requiring pharmacy permission prior to visiting wards. When he had visited the wards at the hospital this had always been with the permission of the ward managers.

Following receipt of the allegation that copies of the materials were still in use in other parts of the country, a further email requesting repeated confirmation of zero stock was sent out to the field-force and replies confirming zero stock were currently being collated.

PANEL RULING

The Panel noted that the parties' accounts of events differed. Denfleet had received a copy of the booklet 'WHO will pay the price for generic clozapine?' from staff in the pharmacy at the hospital allegedly given to them recently by the Novartis representative.

No evidence had been provided by the complainant to show that recently the hospital had a policy for visiting representatives nor that if such a policy existed that it had not been followed.

On the basis of the information before it the Panel decided that it had no option other than to rule no breach of Clauses 15.2 and 15.4 of the Code.

2 Page 8 headed 'What does "bioequivalent" actually mean?'

Denfleet referred to the section entitled 'What do the studies show?' (Denfleet mistakenly referred to page 6 whereas the section at issue appeared on page 8). This was followed by 'Evidence from several pharmacokinetic studies looking at bioequivalence have shown conflicting results'.

This page was similar to the page at issue in point A3 above.

COMPLAINT

Denfleet alleged that the section 'What do the studies show?' contained misleading and inaccurate information. By definition, pharmacokinetics was the study of the absorption, distribution, metabolism and excretion of medicines. The studies appearing on this page Kluznik *et al*, Mofsen and Balter and Price did not examine the pharmacokinetic parameters required to determine bioequivalence. Kluznik 2001 measured plasma concentrations of clozapine. However, the study did not show a significant difference in mean clozapine levels. The studies presented by Mofsen and Balter and Price did not present any of the pharmacokinetic parameters required for examining bioequivalence. Denfleet alleged that the statement 'Evidence from several pharmacokinetic studies …' was inaccurate, misleading and not supported by the studies presented.

RESPONSE

Novartis submitted that part of its response to point A3 above covered this point.

PANEL RULING

The Panel noted that the studies cited on the page in question were not pharmacokinetic studies as such. Mofsen and Balter presented seven case studies of patients in long-term residential care who experienced a relapse of psychotic symptoms when their therapy was switched from branded clozapine to a generic formulation. Kluznik *et al* studied the clinical effects of a randomised switch of patients from Clozaril to generic clozapine. Serum concentrations were measured. Price was taken from a discussion at a symposium which described a switch of patients from Clozaril to generic clozapine. The claim 'Evidence from several pharmacokinetic studies looking at bioequivalence have shown conflicting results' followed by a description of the three studies was thus misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 of the Code were ruled.

3 Claim '30% of the cost of plasma drug concentration monitoring (required while titrating dose) is covered by the CPMS'

Pages 10 and 11 provided details beneath the heading on page 10 'How will the Clozaril Patient Monitoring Service (CPMS) support you?' The claim at issue appeared on page 11 under the subheading 'The comprehensive CPMS package'. This was similar to point A4 above.

COMPLAINT

Denfleet alleged that one of the listed features of the comprehensive CPMS package that '30% of the cost of plasma drug concentration monitoring (required while titrating dose) is covered by the CPMS' was misleading and inaccurate in breach of Clause 7.2 and 7.4.

Denfleet stated that clozapine dosage was normally adjusted according to clinical response and adverse effect profile. The measurement of clozapine plasma concentrations was useful in assessing compliance, optimising therapy and minimising toxicity. Plasma drug level monitoring was not required whilst titrating the dose.

RESPONSE

Novartis stated that the text 'required when titrating the dose' had been removed from future materials.

PANEL RULING

The Panel noted that the Clozaril SPC stated that white blood cell (WBC) count and differential blood counts must be performed within 10 days prior to initiating Clozaril treatment to ensure that only patients with WBC counts and absolute neutrophil count (ANC) within certain given parameters received the medicine. After the start of treatment the WBC and ANC must be monitored weekly for the first 18 weeks of therapy and at least every four weeks thereafter throughout treatment. The use of Clozaril was restricted to patients, physicians and nominated pharmacists registered with the CPMS.

Pages 10 and 11 of the booklet referred to monitoring. The only detailed information about monitoring was in the claim at issue which implied that monitoring was only required when titrating the dose and only plasma drug concentration monitoring was necessary. This was not so. The SPC required WBC count and ANC monitoring at different frequencies depending on how long the patient had been taking Clozaril. The maximum period was at least every four weeks.

The Panel was very concerned that the statement in the booklet gave a very different impression of the monitoring requirements compared to those in the SPC. The statement at issue might compromise patient safety. The Panel considered the statement was misleading and not capable of substantiation as alleged. Breaches of Clauses 7.2 and 7.4 of the Code were ruled.

During its consideration of this case the Panel noted that both booklets bore the same reference number (CLZ/03/78). The Guidelines on Company Procedures Relating to the Code of Practice recommended that a particular reference number should relate to only one item of promotional material. The Panel requested that Novartis be advised of its concerns in this regard.

Complaint received **23 June 2004**

Case completed **24 August 2004**

PRIMARY CARE TRUST MEDICINES MANAGEMENT FACILITATOR v PFIZER

Conduct of representative

The medicines management facilitator at a primary care trust (PCT) stated that a surgery had reported that at a recent practice meeting the local Pfizer representative informed those present that Pfizer was working with the PCT on an audit of COX-2 medicines and comparing the prescribing of COX-2s with National Institute of Clinical Excellence (NICE) guidelines. Pfizer had not approached the PCT prescribing support team about any such activity, and the PCT prescribing support team had not agreed it; nor was it aware of the work Pfizer was seeking to undertake.

In commenting on Pfizer's response the complainant stated that one of her team had recently carried out an audit of COX-2 prescribing at the local surgery in question and was doing similar audits elsewhere. The PCT prescribing lead was concerned that practices would be reluctant to work with PCT staff in a COX-2 audit if Pfizer had undertaken similar work in their practice, particularly if they considered that Pfizer was working with the complainant's approval.

The complainant was surprised that the representative wished to meet the PCT prescribing lead with a view to preparing local guidelines. Draft guidelines for use of COX-2s were in development and the PCT prescribing lead was aware of this.

The complainant also asked the PCT prescribing lead to comment on the response. The PCT prescribing lead stated that she joined the meeting before a presentation by a consultant surgeon. In summing up the representative stated that Pfizer was interested in carrying out audits in practices relating to COX-2 and NICE guidance and was helping the PCT in this way. After the meeting the PCT prescribing lead asked the representative who she was working with in the PCT. One of the prescribing advisors was named but not necessarily by the representative. The PCT prescribing lead arranged a follow-up meeting with the representative and contacted the complainant to see if she had set anything up with Pfizer, which she confirmed she had not. Hence the complaint.

The Panel noted that the parties' accounts differed. The complainant alleged that the representative had stated at a meeting that Pfizer was working with the PCT on a COX-2 audit. The representative and the PCT prescribing lead had spoken at the end of the meeting as the representative was packing up. The representative asked if she and a Pfizer colleague could meet the PCT prescribing lead to discuss how Pfizer could work in partnership in producing local COX-2 guidelines. The representative remembered the meeting as brief; a few seconds rather than minutes. She could not recall what exactly had been said but was sure that she did not state that Pfizer was doing any audits within the PCT. The Panel noted the PCT prescribing lead's submission that when summing up the representative had stated that Pfizer was interested in carrying out audits and 'was helping the PCT in this way'.

The Panel considered that it was beholden upon representatives to be abundantly clear when explaining the relationship between their companies and local organisations such as PCTs to local GPs. Nonetheless, given the parties' differing accounts the Panel was not in a position to determine what had happened. The Panel was thus obliged to rule no breach of the Code.

The medicines management facilitator at a primary care trust (PCT) complained about the conduct of a representative from Pfizer Limited.

COMPLAINT

The complainant stated that she had received a report from a surgery that at a recent practice meeting the local Pfizer representative informed those present that Pfizer was working with the PCT on an audit of COX-2 medicines and comparing the prescribing of COX- 2 medicines with National Institute of Clinical Excellence (NICE) guidelines.

This surprised the PCT prescribing lead (a partner at the practice) and the complainant. Pfizer had not approached the PCT prescribing support team about any such activity. Needless to say, the PCT prescribing support team had not agreed it. If it was to authorise this sort of activity by any pharmaceutical company the PCT team would notify practices as appropriate and would decide on the audit to be undertaken and the interpretation of the NICE guidance.

Not only had the PCT prescribing support team not authorised the 'audit', it was not aware of the work Pfizer was seeking to undertake.

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

RESPONSE

Pfizer agreed that the representative had arranged a meeting at the surgery in question where clinical education sessions were held monthly. A consultant orthopaedic surgeon spoke at the meeting about 'Hip reshaping' to five GPs, a nurse and a physiotherapist.

Prior to the meeting, the representative provided refreshments and gave short presentations on Celebrex, Detrusitol XL and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale. Everybody except the PCT prescribing lead was present for this part of the meeting. The PCT prescribing lead arrived at the meeting just before the presentation commenced (at approximately 7.25 pm).

After the speaker's presentation the representative closed the meeting. Whilst packing up, the representative spoke with the PCT prescribing lead. The representative was particularly keen to speak with the PCT prescribing lead as she was a member of the professional executive committee (PEC) of the PCT. The representative wanted to discuss ways in which she and the Pfizer primary care account manager (PCAM) could work more closely with the PCT prescribing lead and the PCT than the representative was able to do. The Pfizer PCAM would be able to discuss with members of the PCT ways in which Pfizer could work with them to explore care pathways and guidelines, in particular the PCT's approach to NICE guidelines on the use of COX-2 inhibitors. The PCT prescribing lead agreed to see the representative and the Pfizer PCAM at a later date and asked the representative to arrange a meeting. The representative stated that, during her conversation with the PCT prescribing lead, the representative wanted to distinguish that by having the Pfizer PCAM there, Pfizer would be able to discuss how to work at a more strategic level with the PCT.

The following day the representative booked an appointment for the next month with the PCT prescribing lead but the meeting never occurred because when the representative arrived at the surgery the PCT prescribing lead knew nothing about the meeting.

The representative described the conversation with the PCT prescribing lead at the monthly clinical meeting as brief and of the order of seconds rather than minutes. The representative did not remember the exact duration of the conversation or her exact words; she might have said 'guidelines', 'partnership' and 'work at PCT level' with reference to the possible meeting with the Pfizer PCAM. The representative did not state that Pfizer was doing any audits within this PCT. The representative had not had previously met the PCT prescribing lead and she wished to make the most of her opportunity to talk to her.

Pfizer considered that the representative's conversation with the PCT prescribing lead was probably misinterpreted. The representative had not intended to attempt to mislead. The representative knew that the PCT prescribing lead had a role within the PCT as a member of the PEC and clearly had nothing to gain from implying any existing cooperative work between the PCT and Pfizer. Both the PCT prescribing lead and the representative would clearly have known that no such work was going on. Pfizer noted that the complaint came from the PCT prescribing adviser, who was not present at the meeting.

The representative considered that she had behaved appropriately and had upheld the high standards required both by Pfizer and by the Code. With regard to Clauses 9.1 and 15.2, Pfizer considered that the representative had maintained high standards of ethical conduct and complied with all relevant requirements of the Code and there had been no breach of the Code. With regard to Clause 2 of the Code, Pfizer did not consider that the representative had acted in a manner to bring discredit upon, or reduce confidence in, the pharmaceutical industry.

Pfizer concluded that this was a misunderstanding between both parties during a short conversation and that there was no case to answer. Pfizer deeply regretted that the perceived activity of the representative had given rise to such a complaint.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant noted that she had complained because the PCT prescribing lead was concerned that Pfizer was claiming to be working with the PCT on audits in this field when she knew that this was not the case. Any agreements with pharmaceutical companies to undertake such work in the PCT would be agreed by the complainant in conjunction with the medicines management committee. One of the complainant's team had recently carried out an audit of COX-2s at the surgery and was doing similar audits elsewhere. The PCT prescribing lead was concerned that practices would be reluctant to work with PCT staff in a COX-2 audit if Pfizer had undertaken similar work in their practice, particularly if they considered that Pfizer was working with the complainant's approval.

The complainant was surprised that the representative wished to meet the PCT prescribing lead with a view to preparing local guidelines. The complainant understood that both the Pfizer PCAM and the local representatives were aware that guidelines were drawn up collaboratively under the auspices of the area prescribing committee and not by the individual PCTs. Draft guidelines for use of COX-2s were in development and the PCT prescribing lead was aware of this. The local view was that it was not appropriate for pharmaceutical companies to be involved in the development of guidelines.

The complainant also asked the PCT prescribing lead to comment on the response. The PCT prescribing lead agreed that she joined the meeting before the presentation. The presentation was appropriate and well balanced. Pfizer had missed out the fact that, in summing up to the general group, the representative stated that Pfizer was interested in carrying out audits in practices relating to COX-2 and NICE guidance and was helping the PCT in this way. After the meeting the PCT prescribing lead asked the representative about who she was working with in the PCT. One of the prescribing advisor's names was mentioned, but not necessarily by her. The PCT prescribing lead arranged a meeting with the representative as a follow-up and contacted the complainant to confirm that she had not set anything up with Pfizer, which she confirmed. Hence the complaint.

The PCT prescribing lead also stated that one of the partners present had mentioned to the complainant that he thought Pfizer was doing work on behalf of the PCT, which suggested this had been discussed with him as well. The PCT prescribing lead was very concerned that these sorts of messages contravened the work the PCT was supporting – indeed it was rolling out its own COX-2 audit.

PANEL RULING

The Panel noted that the parties' accounts differed; it was difficult in such cases to know exactly what had

transpired. A judgement had to be made on the available evidence bearing in mind that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint.

The complainant alleged that the representative had stated at a meeting that Pfizer was working with the PCT on an audit of COX-2 medicines. The representative and the PCT prescribing lead had spoken at the end of the meeting as the representative was packing up. The representative asked if she and her colleague (the Pfizer PCAM) could meet the PCT prescribing lead to discuss how Pfizer could work in partnership in producing local COX-2 guidelines. The representative's recollection was that the meeting was brief; a few seconds rather than minutes. She could not recall the exact wording used in her conversation with the PCT prescribing lead but was sure that she did not make a statement that Pfizer was doing any audits within the PCT. The Panel noted the PCT prescribing lead's submission that when summing up to the general group the representative had stated that Pfizer was interested in carrying out audits and 'was helping the PCT in this way'.

The Panel considered that it was beholden upon representatives to be abundantly clear when explaining the relationship between their companies and local organisations such as PCTs to local GPs. Nonetheless, given the parties' differing accounts the Panel was not in a position to determine what had happened. The Panel was thus obliged to rule no breach of Clauses 2, 9.1 and 15.2 of the Code.

Complaint received **25 June 2004**

Case completed **27 September 2004**

CASE AUTH/1605/7/04 *NO BREACH OF THE CODE*

CONSULTANT PHARMACIST v LUNDBECK

Cipralex journal advertisement

A consultant pharmacist complained about a journal advertisement for the antidepressant Cipralex (escitalopram) issued by Lundbeck. Cipralex was a selective serotonin reuptake inhibitor (SSRI).

The advertisement was headed 'Then I saw her face. Now I'm a believer' and in the complainant's view showed an attractive young woman with a very young child who seemed delighted to see her general practitioner who had prescribed her Cipralex. The patient was clearly a young mother and the advertisement thus implied that Cipralex was suitable for this particular target group. There was clearly a possibility that this woman might wish to conceive especially now she was so much better being on Cipralex. The complainant alleged that this contradicted the statements in the British National Formulary – Pregnancy, 'Antidepressant SSRI; toxicity in animal studies with escitalopram' and in the Cipralex summary of product characteristics (SPC), 'Pregnancy For escitalopram no clinical data are available regarding exposed pregnancies. In rat reproductive toxicity studies performed with escitalopram, embryo-fetoxic effects, but no increased incidence of malformations, were observed. The risk to humans is unknown'. In the complainant's view the advertisement implied a degree of safety that was at odds with the above statements. The complainant queried whether Cipralex should be used at all in women of childbearing age. Should it be advertised as safe in this group?

The Panel noted that Cipralex SPC stated that there were no clinical data available regarding exposed pregnancies. In rat reproductive toxicity studies, reduced foetal weight and a reversible delay in ossification were observed at exposures in terms of AUC in excess of the exposure achieved during clinical use. No increased frequency of malformations was noted. The risk for humans was unknown. The SPC further stated that Cipralex should not be used during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

The Panel noted that Cipralex was not contraindicated during pregnancy and considered that prescribers would be very familiar with the principles of prescribing in women of childbearing age.

The advertisement in question showed a young woman with a small child apparently sitting in a doctor's waiting room along with a mixed group of other patients. There was no implication that the young woman was pregnant or might wish to be. The Panel decided that the advertisement was not misleading with regard to the safety of Cipralex during pregnancy as alleged. The Panel further considered that the advertisement did not promote Cipralex in a manner which was inconsistent with the particulars listed in its SPC. No breach of the Code was ruled.

A consultant pharmacist complained about a journal advertisement (ref 0104/ESC/501/070) for the antidepressant Cipralex (escitalopram) issued by Lundbeck Ltd. Cipralex was a selective serotonin reuptake inhibitor (SSRI).

COMPLAINT

The complainant noted that the advertisement was headed 'Then I saw her face. Now I'm a believer'. The advertisement showed an attractive young woman with a very young child who seemed

delighted to see her general practitioner who had prescribed her Cipralex. The patient was clearly a young mother. The advertisement therefore implied that Cipralex was suitable for this particular target group. There was clearly a possibility that this woman might wish to conceive, especially now she was so much better being on Cipralex. The complainant considered that this contradicted the statements in the British National Formulary (BNF) March 2004 Appendix 4 Pregnancy, 'Antidepressant SSRI; toxicity in animal studies with escitalopram' and in the Cipralex summary of product characteristics (SPC), 'Pregnancy For escitalopram no clinical data are available regarding exposed pregnancies. In rat reproductive toxicity studies performed with escitalopram, embryo-fetoxic effects, but no increased incidence of malformations, were observed. The risk to humans is unknown'. In the complainant's view the advertisement implied a degree of safety that was at odds with the above statements. The complainant queried whether Cipralex should be used at all in women of childbearing age. Should it be advertised as safe in this group?

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

RESPONSE

Lundbeck did not consider that its promotion of Cipralex was either misleading or inconsistent with the Cipralex SPC. It was important to separate being female and of childbearing age from being female and pregnant/or wishing to become pregnant.

Lundbeck considered that it was appropriate to promote Cipralex in the treatment of major depressive episodes in adults, both female and male aged 18 or older in accordance with the terms of its marketing authorization. The company noted a two fold greater prevalence of major depressive disorder in women than in men, with an onset between the ages of 20 and 50 in 50% of all patients. The use of a woman in the advertisement was therefore not inappropriate. The use of Cipralex during pregnancy was not contraindicated, and the warnings regarding such use were clearly stated in section 4.6 of the SPC and the prescribing information ie 'Pregnancy and Lactation: As safety during human pregnancy and lactation has not been established, careful consideration should be given prior to use in pregnant women. It is expected that escitalopram will be excreted into breast milk. Breast-feeding women should not be treated with escitalopram'.

The advertisement did not imply that the patient might be/or wish to become pregnant. The advertisement showed a woman of childbearing age. Lundbeck would not promote the use of Cipralex to patients who were, or wished to become, pregnant. The patient was not depicted in a setting that implied that she was wishing to become pregnant eg an antenatal clinic, nor was she, for example, holding a pregnancy detection kit. The complainant made the far-reaching premise that the patient was or wished to become pregnant and arrived at his own conclusion.

Lundbeck noted the important point raised by the complainant ie should any medicine that might potentially harm an unborn child be promoted to women of childbearing age? There were perhaps only a handful of medicines that were considered 'safe' to use during pregnancy and the majority of medicines carried warnings and precautions for their use in pregnancy eg all SSRIs, proton pump inhibitors, anti-hypertensives, anti-epileptics and analgesics including the commonly prescribed non-steroidal anti-inflammatories.

The best way to avoid potentially harming an unborn child as a result of treatment was for a patient not to take a medicine in the first place. A physician prescribing any medicine to a woman of childbearing age would automatically weigh up the risk/benefit for the patient and advise the woman on the risks involved were she to consider pregnancy or indeed become pregnant.

Lundbeck considered that it had fulfilled its obligation of informing the prescriber of the warning concerning pregnancy by providing the prescribing information. The decision and responsibility to prescribe a medicine eg Cipralex, taking into consideration the fact that a woman might at some future stage become pregnant, rested with the clinician. Furthermore, the pharmacist dispensing the medicine had an ethical obligation to perform a professional assessment of the prescription, including the suitability of the medicine for the patient ie by asking if the patient was pregnant.

If one were to make the premise that the warnings displayed in the prescribing information were insufficient, one would have to conclude that the use of a picture of a female of childbearing age in the promotion of the majority of medicines was also incorrect.

In summary, Lundbeck considered that the advertisement was neither misleading nor inconsistent with the particulars listed in the Cipralex SPC.

PANEL RULING

The Panel considered that it was a well established principle that medicines should be prescribed during pregnancy only if the expected benefit to the mother outweighed the potential risk to the foetus and that all medicines should be avoided if possible during the first trimester.

The Cipralex SPC stated that there were no clinical data available regarding exposed pregnancies. In rat reproductive toxicity studies, reduced foetal weight and a reversible delay in ossification were observed at exposures in terms of AUC in excess of the exposure achieved during clinical use. No increased frequency of malformations was noted. The risk for humans was unknown. The SPC further stated that Cipralex should not be used during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

The Panel noted that Cipralex was not contraindicated during pregnancy and considered that prescribers would be very familiar with the principles of prescribing in women of childbearing age.

The advertisement in question showed a young woman with a small child apparently sitting in a doctor's waiting room along with a mixed group of other patients. There was no implication that the young woman was pregnant or might wish to be. The Panel decided that the advertisement was not misleading with regard to the safety of Cipralex during pregnancy as alleged. No breach of Clause 7.2 was ruled. The Panel further considered that the advertisement did not promote Cipralex in a manner which was inconsistent with the particulars listed in its SPC. No breach of Clause 3.2 was ruled.

Complaint received **7 July 2004**

Case completed **23 August 2004**

CASE AUTH/1611/8/04

MEDIA/DIRECTOR v BAYER

Promotion of Avelox

An article in the Drug and Therapeutics Bulletin, entitled 'Moxifloxacin – a new fluoroquinolone antibacterial' criticized the claim 'Rapid relief from chest infections' made by Bayer about Avelox (moxifloxacin). In accordance with established procedure the matter was taken up by the Director as a complaint under the Code. In response to the complaint Bayer provided a journal advertisement, a leavepiece and a detail aid, all of which featured the claim at issue.

The Drug and Therapeutics Bulletin article began by noting that Avelox was licensed for the oral treatment of adults with community-acquired pneumonia, acute exacerbation of chronic bronchitis or acute sinusitis. The authors further noted that the claim 'Rapid relief from chest infections' was based on patients' self-reported secondary-outcome data from one unblinded, randomised, controlled trial (Kreis *et al* 2000) and on unblinded, non-randomised, observational studies (Miravitlles *et al* 2003; Miravitlles *et al* 2004 and Landen and Bauer 2001). The authors stated that these studies did not provide convincing evidence that Avelox relieved respiratory tract infections as quickly as, or faster than standard antibiotics and concluded that on published clinical evidence Avelox offered no compelling advantages over established treatments. The authors considered that claims that Avelox provided 'Rapid relief from chest infections' were unsubstantiated, potentially misleading and should be withdrawn.

The Panel noted that the authors of each of the four studies which Bayer submitted supported its claim 'Rapid relief from chest infections' had referred to the rapid relief of symptoms associated with Avelox therapy. In this regard the Panel noted the conclusion of Miravitlles *et al* (2004) that as Avelox was associated with a more rapid remission of symptoms compared with co-amoxiclav or clarithromycin then 'randomised, experimental studies need to be designed to corroborate the hypothesis proposed in this study that antibiotics that induce a more rapid bacteriological eradication are associated with a similarly more rapid clinical cure'. Bayer had submitted that the claim was intended to inform the reader that Avelox rapidly relieved the symptoms of infection. However, as the claim did not refer to symptomatic relief the Panel considered that it could be read to mean that Avelox rapidly cured chest infections *per se* ie that there was a rapid and complete eradication of micro-organisms. No data in this regard had been submitted. In the Panel's view, patients whose symptoms had been relieved could still have a chest infection. The Panel considered that the claim was ambiguous and thus misleading as alleged and had not been substantiated. Breaches of the Code were ruled.

An article in the Drug and Therapeutics Bulletin, August 2004, entitled 'Moxifloxacin – a new fluoroquinolone antibacterial' criticized a claim made by Bayer plc about Avelox (moxifloxacin). In accordance with established procedure the matter was taken up by the Director as a complaint under the Code.

Bayer provided a journal advertisement (ref 2AVEL87), a leavepiece (ref 4AVEL004) and a detail aid (ref 4AVEL001); all of the materials featured the Avelox product logo which incorporated the strapline 'Rapid relief from chest infections'.

COMPLAINT

The Drug and Therapeutics Bulletin article began by noting that Avelox, the latest fluoroquinolone antibacterial to be launched in the UK, was licensed for the oral treatment of adults with community-acquired pneumonia, acute exacerbation of chronic bronchitis or acute sinusitis. The article, in addition to reviewing the place of Avelox in treating patients with respiratory tract infections, noted that promotional materials stated that the product provided 'rapid relief from chest infections'. The authors noted that this claim, however, was based on patients' self-reported secondary-outcome data from one unblinded, randomised, controlled trial (Kreis *et al* 2000) and on unblinded, non-randomised, observational studies (Miravitlles *et al* 2003; Miravitlles *et al* 2004 and Landen and Bauer 2001). The authors stated that because of the studies' design, they could not provide convincing evidence that Avelox relieved respiratory tract infections as quickly as, or faster than standard antibacterial treatments for these conditions. The authors concluded that on published clinical evidence, Avelox offered no compelling advantages over established treatments for these conditions. The authors stated that in their view, claims that Avelox provided 'Rapid relief from

chest infections' were unsubstantiated, might mislead prescribers and should be withdrawn.

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

RESPONSE

Bayer stated that Avelox, launched in the UK at the end of March 2003, was licensed for the treatment of acute exacerbations of chronic bronchitis (AECB), community acquired pneumonia (CAP, except severe cases) and acute bacterial sinusitis (adequately diagnosed).

The claim 'Rapid relief from chest infections' was a strapline, which accompanied the Avelox logo.

The intention of the claim was to succinctly communicate to health professionals the therapeutic area where the product could be used along with a product attribute. On all the materials where the claim appeared prescribing information was also provided. The claim therefore communicated that Avelox treated chest infections and that when it was used the symptoms of the infection were relieved rapidly.

Bayer summarised the clinical data to support the claim. The data had been published in peer-reviewed journals.

Miravitlles *et al* (2003) was a 2 year observational study in 441 outpatients with AECB. In the first year no Avelox therapy was prescribed; in the second year, 50% of patients were treated with Avelox. One hundred and eleven exacerbations were treated with Avelox and 503 were treated with comparator antibiotics. The mean time to recovery was 4.6 days for Avelox and 5.8 days for the comparators (p=0.006). The authors stated that 'The significantly more rapid symptom relief and time to recovery associated with moxifloxacin therapy may be attributable to the unique aspects of moxifloxacin's interaction with the bacteria and host'.

Landen and Bauer was a post-marketing study in 2188 patients with CAP requiring hospital admission. All patients received 400mg moxifloxacin once daily for up to 10 days. 93.4% of patients were cured or improved after treatment; 60.4% demonstrated distinct improvement by day 3 of treatment (90% by day 5) and 73.7% were symptom free by day 7 (87.0% by day 10). The authors stated that 'The results of this study confirm the evidence from clinical studies indicating that moxifloxacin 400mg once daily is an effective and well tolerated therapy for CAP providing rapid and comprehensive resolution of symptoms in a broad range of patients'.

Miravitlles *et al* (2004) was a primary care observational non-randomised study in 1456 patients with AECB or AE-COPD – Avelox 400mg once daily for 5 days was compared with co-amoxiclav 625mg three times daily for 10 days or clarithromycin 500mg twice daily for 10 days. Clinical cure rates observed on day 3 were Avelox 20%, co-amoxiclav 9.6% and clarithromycin 6.5% (p<0.001). Clinical cure rates observed on day 5 were; Avelox 49%, co-amoxiclav 26.5% and clarithromycin 30% (p<0.001). Clinical cure rates were similar at day 10. The authors stated that the 'results of this study suggest that the antibiotic treatment of exacerbations of chronic bronchitis and COPD with moxifloxacin is associated with a more rapid remission of the symptoms to that achieved with co-amoxiclav or clarithromycin'.

Kreis *et al* was an observational study of 401 patients with AECB. Avelox 400mg once daily for 5 days was compared with azithromycin 500mg on day one and 250mg once daily for 4 days. Avelox-treated patients reported feeling better significantly faster than azithromycin-treated patients (p=0.0236). More patients in the Avelox group reported symptomatic relief by day 3 than did patients in the azithromycin group (p=0.012). The authors stated that 'Patients treated with moxifloxacin reported faster symptom relief and returned to normal activities more rapidly'.

Bayer stated that although these data suggested an advantage of Avelox over a number of comparators, the claim itself did not draw a direct comparison with other therapies. Bayer considered that its use of these studies was a conservative interpretation of the results and conclusions of the authors.

Bayer noted that the Drug and Therapeutics Bulletin noted that the claim was based on patients' self-reported secondary-outcome data from one unblinded, randomised, controlled trial and on unblinded, non-randomised, observational studies. However, the Code did not state that all published references must be from randomised double-blind studies. These four studies had been conducted by three lead authors and published in two peer-reviewed journals over the past four years and showed that treatment with Avelox resulted in rapid symptom relief. Furthermore, no trial had been published in a peer review journal that had compared Avelox with another agent that had shown more rapid symptomatic relief with the other agent.

Bayer did not consider that the claim 'Rapid relief from chest infections' was in breach of Clause 7.2 or 7.4 of the Code.

PANEL RULING

The Panel noted that Bayer had submitted that four studies supported its claim 'Rapid relief from chest infections'. The authors in each of the studies had referred to the rapid relief of symptoms associated with Avelox therapy. In this regard the Panel noted the conclusion of Miravitlles *et al* (2004) that the results suggested that 'the antibiotic treatment of exacerbations of chronic bronchitis and COPD with moxifloxacin is associated with a more rapid remission of the symptoms to that achieved with co-amoxiclav or clarithromycin. On this basis, randomised, experimental studies need to be designed to corroborate the hypothesis proposed in this study that antibiotics that induce a more rapid bacteriological eradication are associated with a similarly more rapid clinical cure'. Bayer had submitted that the claim was intended to inform the reader that Avelox rapidly relieved the symptoms of infection. The claim, however, did not refer to symptomatic relief. The Panel thus considered that the claim could be read to mean that Avelox rapidly

cured chest infections *per se* ie that there was a rapid and complete eradication of micro-organisms. No data in this regard had been submitted. In the Panel's view, patients whose symptoms had been relieved could still have a chest infection. The Panel considered that the strapline was ambiguous and thus misleading as alleged and had not been substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

Proceedings commenced 4 August 2004

Case completed 16 September 2004

CASE AUTH/1612/8/04

SCHWARZ PHARMA v STIEFEL

Promotion of Duac

Schwarz Pharma complained about the claim 'Significantly preferred by patients to Benzamycin' used by Stiefel to promote Duac (clindamycin/benzoyl peroxide gel). Schwarz marketed Benzamycin (erythromycin/benzoyl peroxide gel). Duac and Benzamycin were both indicated for the treatment of acne.

Schwarz alleged that the claim implied that Duac was preferred on all assessed criteria; the claim did not clarify what the criteria were. The data on file to which the claim was referenced stated that 'subjects preferred [Duac] over Benzamycin on virtually each attribute and on an overall basis'. It appeared that 'preference' therefore encompassed all assessed criteria, and was not limited to the question 'Which product did you prefer overall?'. On further review of the data on file, of the 14 questions plus sub-questions there were no statistically significant differences for 'feel', 'stinging' and 'greasiness' at visit 1, and for ease of make-up application at visits 1 and 2. The reported extent of greasiness appeared to favour Benzamycin, with statistical significance at visit 2. Therefore, not all attributes were assessed in favour of Duac. It was not clear from the claim in what ways Duac was 'significantly preferred'. Schwarz alleged that the claim did not accurately reflect the results of the study, and therefore could not be substantiated and was misleading.

Schwarz noted that the data on file referred to a one week study with assessments being performed immediately after first application and on a second visit one week later. Acne treatment, however, normally lasted three to six months, which was not reflected by this study. The claim made no reference to the study duration, which therefore might be considered misleading and not accurately reflecting the evidence. Patient preference might be influenced by efficiency outcomes as well as the physical attributes of products. Patients required a therapy to alleviate their symptoms, and this might impact on any preference for a product.

It only became apparent on review of the data on file that the comparison related to practical attributes and not clinical outcomes. Schwarz also noted that it could not tell from the data on file if the study had only included patients consistent with the licensed indication.

Schwarz alleged that the information presented was not balanced and appeared nonsensical. This highlighted fundamental issues with the design of the study. Schwarz also alleged that the claim 'Significantly preferred by patients to Benzamycin' based on the data on file, in its various representations, was ambiguous and, as a comparative claim was misleading.

The Panel noted that Duac was indicated for the treatment of mild to moderate acne. The objective of the study from which the claim at issue was derived was to compare the consumer acceptability of Duac and Benzamycin on the basis of immediate perception of aesthetic attributes and after one week's use. The Panel noted Stiefel's submission that almost all of the 51 patients who took part in the study had mild to moderate acne; one patient was borderline and fell just outside the definition of moderate. Most but not all of the parameters measured showed a benefit for Duac compared with Benzamycin. The claim 'Significantly preferred by patients to Benzamycin' was based on the answer to the question 'which product did you prefer overall?'.

In two leavepieces the claim at issue immediately followed two claims which referred to the efficacy of Duac and its *in vivo* antimicrobial activity respectively. In the printed copy of a product monograph the claim appeared as the last of five bullet points the first four of which referred to efficacy and tolerability. The Panel noted that there was no indication in any of the materials that the claim at issue was derived from a one week study and was based only on cosmetic and practical considerations and not on any measures of efficacy. In the Panel's view some readers would assume that the claim referred to the longer term use of the two products; given the context in which it appeared some might also assume that a measure of efficacy was included. The unqualified claim did not allow the reader to judge its clinical significance. The Panel considered that the claim was misleading in that regard and ruled breaches of the Code.

Schwarz Pharma Limited complained about the promotion of Duac (gel containing clindamycin 1% and benzoyl peroxide 5%) by Stiefel Laboratories (UK) Ltd. The claim at issue 'Significantly preferred by patients to Benzamycin' and/or related claims appeared in two leavepieces (refs D: E3128UK and D:E3130UKc) and in a product monograph (ref D:E3002UK) as presented on a CD-ROM. Schwarz marketed Benzamycin (gel containing erythromycin 3% and benzoyl peroxide 5%). Duac and Benzamycin were both indicated for the treatment of acne.

COMPLAINT

Schwarz alleged that the claim 'Significantly preferred by patients to Benzamycin' implied that Duac was preferred on all assessed criteria; the claim did not clarify the criteria. The data on file to which the claim was referenced stated that 'subjects preferred Clindoxyl Gel over Benzamycin on virtually each attribute and on an overall basis'. It appeared that 'preference' therefore encompassed all assessed criteria, and was not limited to the one question 'Which product did you prefer overall?'. Of the 14 questions plus sub-questions, there were no statistically significant differences for 'feel', 'stinging' and 'greasiness' at visit 1, and for ease of make-up application at visits 1 and 2. The reported extent of greasiness appeared to favour Benzamycin, with statistical significance at visit 2. Therefore, not all attributes were assessed in favour of Duac. It was not clear from the claim in what ways Duac was 'significantly preferred'. Schwarz alleged that the claim did not accurately reflect the results of the study, and therefore could not be substantiated and was misleading.

Schwarz noted that the duration of the study which comprised the data on file was one week, with assessments being performed immediately after first application and on a second visit one week later. Acne treatment, however, would be expected to last in the order of three to six months, which was not reflected by this study. The claim made no reference to the duration of the study, which therefore might be considered misleading and not accurately reflecting the evidence. Patient preference might not be solely influenced by the physical attributes of products, but might also be influenced by efficacy outcomes. Patients required that a therapy alleviated their symptoms, and this might impact on any preference for a product. No demonstration of such an influence, or lack of influence, of efficacy was presented in the data on file.

In intercompany correspondence, Stiefel had suggested that the claim was a straightforward statement which summarised the outcome of a well-designed study and that such 'sensory' studies were usually short-term compared to the longer duration studies for comparison of clinical efficacy. It was not apparent from the claim that this was not a clinical study comparing efficacy outcomes, or that it was a 'sensory' study. Only review of the data on file did it become apparent that the comparison related to practical attributes and not clinical outcomes.

Further, Stiefel had also suggested that it was 'the early perceptions of the cosmetic acceptability of a treatment which were likely to dictate compliance' and that 'Compliance is an important factor in acne treatment and we consider it appropriate to inform prospective prescribers that Duac is favourably perceived by patients, since this means that they are more likely to use the product correctly. Of course, this in turn improves the outcomes outside the strictly enforced regime of a clinical trial'. By Stiefel's own admission, this was not a clinical trial, but consumer patient acceptability, which should be clearly stated with such claims. Stiefel also failed to provide any substantiation regarding early perceptions of cosmetic acceptability and improved compliance, that these perceptions might then lead to correct use of the product and that this might lead to improved compliance.

In the consumer acceptability analysis detailed in the data on file one question asked 'How inconvenient was the requirement to store the product in the refrigerator and apply the product cold?'. This was a leading question that was inappropriate in such a survey as it primed the respondent with a 'negative' impression of one product and influenced responses to other questions. A neutral question with appropriate choices of response would be a more acceptable and valid approach. This leading question that the questionnaire design might be flawed results from the study should be interpreted with caution.

In intercompany correspondence Stiefel had stated that the data on file study included patients consistent with the licensed indication ie moderate to moderately severe acne. This was not apparent from the data on file. However, the UK summary of product characteristics (SPC) stated 'mild to moderate acne vulgaris' with no reference to 'moderately severe' acne. 'Moderate' reflected severity not 'moderately severe'. Therefore, the study did not reflect the licensed indications and should not be used to support any claims. Stiefel's response suggested that a distinction between moderate and moderately severe acne was not precise. However, in a well-designed study, inclusion criteria would be expected to be sufficiently and accurately defined. Stating moderate to moderately severe suggested a distinction in severity. The assertion that both products were used in patients with the same grade of acne 'making the comparison fair' was irrelevant when one product was not licensed in the UK for moderately severe acne. UK clinical practice would likely involve patients with severe acne being prescribed oral antibiotics. Furthermore, there was no substantiation to support Stiefel's assumption that sensory perceptions following use of either product in moderately severe acne would be a more stringent test of their patient acceptability than in patients with mild acne.

In the product monograph on the page entitled 'Patient acceptability', only those attributes with favourable or neutral outcome had been presented. Listing the attribute of greasiness as 'low levels of greasy/oiliness' was misleading as it followed the statement 'Duac Once Daily Gel was preferred to Benzamycin on an overall basis, as well as performing significantly better on all but one of the attributes tested'. According to the data on file, Benzamycin was rated as less greasy compared to Duac to a statistically significant degree at visit 2. The presentation of information did not account for any impact efficacy outcomes over standard treatment durations might have. It was ambiguous to claim that Duac was 'preferred by both men and women on virtually every attribute and on an overall basis'.

Schwarz also alleged that the information presented was not balanced and appeared nonsensical. This highlighted fundamental issues with the design of the study.

Schwarz alleged that the claim at issue based on the data on file, in its various representations, was ambiguous and, as a comparative claim was misleading in breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Stiefel noted that the study in question invited patients to answer a number of questions concerning the acceptability of Duac and Benzamycin. These were: smell, colour, greasiness, spreadability, feel, stinging and application of make up, and the following key questions:

- Which product did you prefer overall?
- Was it more convenient to apply product once a day or twice a day?
- Was it more convenient to apply product from a jar or a tube?
- If both products worked equally well and cost the same, which one would you purchase?

The answer to all of these key questions showed a significant preference for Duac over Benzamycin. Of the eight subsidiary questions yielding 16 tests, ten showed a significant preference for Duac, five showed non-significant preference for Duac. Only one test (greasiness at visit 2) showed a significant preference for Benzamycin. Stiefel considered that the results showed an overwhelming preference for Duac over Benzamycin. The question concerning greasiness was one of several subsidiary questions, clearly, the answers to the key questions confirmed that the individuals concerned preferred Duac overall to Benzamycin. On the basis of these results Stiefel did not consider that the claim was either misleading or ambiguous and was not, therefore, in breach of Clauses 7.2 and 7.3 of the Code.

Stiefel explained that the exchange of correspondence referred to by Schwarz took place between the two companies in January and February 2004. Stiefel had not received a response from Schwarz to its last letter of 13 February, which could be interpreted as tacit acceptance of its position. Nevertheless in the interests of maintaining good relations with Schwarz, Stiefel had decided to revise its literature. It now made the claim 'more cosmetically acceptable than Benzamycin'. Item D:E3128UK was revised in May 2004 and D:E3130UK was the only remaining item of literature containing the claim in question. Both items were used with GPs and dermatologists.

Stiefel noted that a UK Prodigy classification of acne acknowledged the difficulties in classifying acne grades precisely, Prodigy provided the following guideline: 'The classification into mild, moderate or severe acne relies heavily on a subjective assessment. In research, counts of lesions are used to assess severity. This is not practical in general clinical practice, but describing this approach may help to judge severity: mild: fewer than 20 comedones, or fewer than 15 inflammatory lesions, or total lesion count fewer than 30, moderate: 20-100 comedones, or 15-50 inflammatory lesions, or total lesion count 30-125 and severe: more than five cysts, or total comedone count greater than 100, or total inflammatory count greater than 50, or total lesion count greater than 125'.

Applying this definition to the patients in the study in question showed that 51 of the patients fell into the UK classification of mild to moderate acne. One patient was borderline and just outside this particular definition of moderate. Thus the patients used were within the terms of the licenced indication for Duac and the study was a fair and valid comparison, and the promotional claim was valid.

In conclusion, Stiefel submitted that the claim at issue was neither ambiguous nor misleading and it was not in breach of Clauses 7.2 and 7.3 of the Code.

PANEL RULING

The Panel noted that Duac was indicated for the treatment of mild to moderate acne. The objective of the study from which the claim at issue was derived was to compare the consumer acceptability of Duac and Benzamycin on the basis of immediate perception of aesthetic attributes and after one week's use. The Panel noted Stiefel's submission that almost all of the 51 patients who took part in the study had mild to moderate acne; one patient was borderline and fell just outside the definition of moderate. Most of the parameters measured showed a benefit for Duac compared with Benzamycin although after one week patients rated Duac greasier than Benzamycin and there was no difference between the two for 'ease of make-up application'. The claim 'Significantly preferred by patients to Benzamycin' was based on the answer to the question 'which product did you prefer overall?'.

In the two leavepieces the claim at issue immediately followed two claims which referred to the efficacy of Duac and its *in vivo* antimicrobial activity respectively. In the printed copy of the product monograph (the copy provided on a CD-ROM could not be read) the claim appeared as the last of five bullet points; the first four bullet points referred to efficacy and tolerability. The Panel noted that there was no indication in any of the materials that the claim at issue was derived from a one week study and was based only on cosmetic and practical considerations and not on any measures of efficacy. In the Panel's view some readers would assume that the claim referred to the longer term use of the two products; given the context in which it appeared some might also assume that a measure of efficacy was included. The unqualified claim did not allow the reader to judge its clinical significance. The Panel considered that the claim was misleading in that regard and ruled breaches of Clauses 7.2 and 7.3 of the Code.

Complaint received **5 August 2004**

Case completed **29 September 2004**

CASE AUTH/1613/8/04

BAXTER HEALTHCARE v JOHNSON & JOHNSON WOUND MANAGEMENT

Promotion of Quixil

Baxter Healthcare complained that Johnson & Johnson Wound Management had promoted Quixil (human surgical sealant) outwith its licensed indications. Quixil was licensed as supportive treatment to improve haemostasis and to reduce operative and post-operative bleeding and oozing during liver surgery such as liver resection and reduced-size liver transplantation and orthopaedic surgery such as total hip replacement and total knee replacement.

Baxter Healthcare noted that Quixil was displayed and supporting advertising material made available at the Johnson & Johnson stand at a meeting for obstetricians and gynaecologists in Glasgow. The congress only covered topics of interest for gynaecologists and obstetricians and therefore no liver or orthopaedic topics were on the agenda. Baxter Healthcare further noted that similar material was displayed and distributed at the Johnson & Johnson stand during a meeting on surgical trauma skills. The meeting was clearly aimed at trauma surgeons; no liver or orthopaedic topics were on the agenda.

Baxter Healthcare stated that it was unacceptable for Quixil to be promoted to any surgeon outside the fields of liver or orthopaedic surgery. Indeed, such activity could be interpreted as overt encouragement of off-label use of the products which was misleading and exactly the type of activity that reduced confidence in the pharmaceutical industry as a whole.

The Panel noted that Quixil was only licensed for use in liver surgery, such as liver resection and reduced-size liver transplantation, and orthopaedic surgery, such as total hip or knee replacement. In the first instance a Quixil product brochure and administration device had been made available at a meeting for obstetricians and gynaecologists, albeit briefly until they were removed from Johnson & Johnson's stand when the error was noted. A large exhibition panel, headed 'Haemostasis?', however, remained and this included a picture of the Quixil administration device. Given that the device was unique to Quixil and was displayed on a Johnson & Johnson exhibition panel, the Panel considered that even in the absence of the product name the exhibition panel promoted Quixil. The Panel considered that promotion of Quixil to obstetricians and gynaecologists was not in accordance with the particulars listed in the summary of product characteristics (SPC). A breach of the Code was ruled.

The Panel noted that Quixil material had also been made available at a meeting of trauma surgeons. The agenda for the meeting showed that day three began with a liver lecture. In the Panel's view Quixil was thus relevant to the attendees; patients might undergo liver resection following trauma. No breach of the Code was ruled.

Baxter Healthcare Ltd complained about the promotion of Quixil (human surgical sealant) by Johnson & Johnson Wound Management. Quixil was used as supportive treatment to improve haemostasis and to reduce operative and post-operative bleeding and oozing during liver surgery such as liver resection and reduced-size liver transplantation and orthopaedic surgery such as total hip replacement and total knee replacement.

COMPLAINT

Baxter Healthcare noted that Quixil was displayed and supporting advertising material made available at the Johnson & Johnson Gynaecare stand at a meeting for obstetricians and gynaecologists in Glasgow in July. The congress only covered topics of interest for gynaecologists and obstetricians and therefore no liver or orthopaedic topics were on the agenda.

Baxter Healthcare further noted that Quixil and supporting advertising material were displayed and distributed at the Johnson & Johnson stand during a meeting on Definitive Surgical Trauma Skills in London in July. The meeting was clearly aimed at trauma surgeons. Again there were no liver or orthopaedic topics on the agenda during the time that Johnson & Johnson promoted Quixil.

According to Section 4.1 of the summary of product characteristics (SPC) Quixil was licensed for the following therapeutic indications:

'Quixil is used as supportive treatment to improve haemostasis and to reduce operative and post-operative bleeding and oozing during the following procedures:

- liver surgery such as liver resection and reduced-size liver transplantation
- orthopaedic surgery such as total hip replacement and total knee replacement'.

Baxter Healthcare alleged that promotion of the product at the above mentioned congresses constituted promotion outwith its licensed indications in breach of Clause 3.2 of the Code.

The meetings in question were meetings of UK surgical organisations, and attended primarily by UK surgeons – it was therefore unacceptable for Quixil to be promoted to any surgeon outside the fields of liver or orthopaedic surgery. Indeed, such activity could be interpreted as overt encouragement of off-label use of the product which was misleading and exactly the type of activity that reduced confidence in the pharmaceutical industry as a whole. Baxter Healthcare alleged a breach of Clause 2 of the Code.

RESPONSE

Johnson & Johnson stated that the meeting in Glasgow was attended by Johnson & Johnson Wound Management as part of a cross-franchise exhibition stand. Johnson & Johnson provided a copy of an

exhibition panel which did not refer to Quixil, but did contain a picture of the delivery device. Johnson & Johnson submitted that this enabled the panel to be used across a wide variety of meetings.

Johnson & Johnson stated that at the start of the three day meeting the Quixil product brochure was available at the stand and a Quixil applicator was on display. When the manager of the sales representative who had organised the stand arrived he advised that it was inappropriate to display the product in that environment. The literature and product were immediately removed and were not displayed or discussed with regard to obstetric and gynaecological surgery for the remainder of the three day meeting.

Johnson & Johnson agreed that display of Quixil at this meeting was not relevant to the delegates. The company regretted the error and would provide guidelines to its marketing organisation on the suitability of conferences for future promotion of Quixil to avoid recurrence.

Johnson & Johnson provided a copy of the agenda for the meeting about surgical trauma skills and noted that there was a lecture concerning trauma and liver surgery, an indicated use for Quixil. Johnson & Johnson attended this meeting with the full range of Quixil promotional material due to the involvement of both liver and orthopaedic surgeons in the treatment of trauma. Therefore the presence of Quixil at this meeting was appropriate, considering its approved indications.

Following a request for further information, Johnson & Johnson stated that the double-barrelled syringe provided with Quixil was unique to that product.

PANEL RULING

The Panel noted that Quixil was only licensed for use in liver surgery, such as liver resection and reduced-size liver transplantation, and orthopaedic surgery, such as total hip or knee replacement. The Panel considered each meeting separately. In the first instance a Quixil product brochure and administration device had been made available at a meeting for obstetricians and gynaecologists, albeit briefly until they were removed from Johnson & Johnson's stand by the representative's manager when the error was noted. A large exhibition panel, headed 'Haemostasis?', however, remained and this included a picture of the Quixil administration device. Given that the device was unique to Quixil and was displayed on a Johnson & Johnson exhibition panel, the Panel considered that even in the absence of the product name the exhibition panel promoted Quixil. The Panel considered that promotion of Quixil to obstetricians and gynaecologists was not in accordance with the particulars listed in the SPC as alleged. A breach of Clause 3.2 was ruled. The Panel noted that a ruling of a breach of Clause 2 of the Code was a sign of particular censure and reserved for such use. The Panel did not consider that the circumstances warranted a breach of Clause 2.

In the second instance Quixil material had been made available at a meeting of trauma surgeons. The agenda for the meeting showed that day three began with a liver lecture. In the Panel's view Quixil was thus relevant to the attendees; patients might undergo liver resection following trauma. The Panel did not consider that Quixil could only be promoted on the day of the liver lecture as seemed to be implied by Baxter Healthcare. No breach of Clause 3.2 was ruled. It thus followed that there was no breach of Clause 2.

Complaint received **5 August 2004**

Case completed **22 September 2004**

CASE AUTH/1614/8/04

SCRUTINY/DIRECTOR v MERCK SHARP & DOHME

Arcoxia journal advertisement

It was considered during the course of routine scrutiny of journal advertisements that the strapline 'POWER to relieve pain and inflammation in a *broad range of indications*' (emphasis added) in an Arcoxia (etoricoxib) advertisement was broader than the licensed indication for the product and thus inconsistent with the particulars listed in the summary of product characteristics (SPC). This was not accepted by Merck Sharp & Dohme and the matter was accordingly referred to the Code of Practice Panel as a complaint.

Arcoxia was a selective cyclo-oxygenase 2 (COX-2) inhibitor indicated for the symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA) and the pain and signs of inflammation associated with acute gouty arthritis.

The Panel noted that there was nothing in the advertisement to suggest to the prescriber that Arcoxia was only licensed in OA, RA and acute gouty arthritis. The only two claims in the advertisement 'The power to move you' and 'POWER to relieve pain and inflammation in a broad range of indications' appeared stark against the background. The Panel considered that, in the context in which it appeared, the phrase 'broad range of indications' for a COX-2 selective inhibitor might be read by some as meaning that the product could be used for more than just arthritic conditions given that other such medicines could be used for non-arthritic conditions eg acute pain of any origin and primary dysmenorrhoea. The Panel considered that in the advertisement in question the claim was misleading and inconsistent with the particulars listed in the SPC. Breaches of the Code were ruled.

This case arose from the routine scrutiny of journal advertisements. As the matter could not be settled, it was referred to the Code of Practice Panel as a case in accordance with Paragraph 18.4 of the Constitution and Procedure.

The advertisement in question was for Arcoxcia (etoricoxib) issued by Merck Sharp & Dohme and had appeared in Pulse, 14 June 2004. The advertisement featured the headline claim 'The power to move you' superimposed onto the photograph of the bottom of a large waterfall. Along the base of the advertisement ran the strapline 'POWER to relieve pain and inflammation in a broad range of indications' followed by the product logo. Arcoxia was a selective cyclo-oxygenase 2 (COX-2) inhibitor.

COMPLAINT

During the course of routine scrutiny of journal advertisements it was noted that Arcoxia was indicated for the symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA) and the pain and signs of inflammation associated with acute gouty arthritis (summary of product characteristics (SPC)). The advertisement claimed 'POWER to relieve pain and inflammation in a **broad range of indications**' (emphasis added). The unqualified claim appeared to be broader than the licensed indication for the product and thus inconsistent with the particulars listed in the SPC.

It was considered that the claim implied that Arcoxia could be used to treat pain and inflammation generally and not just that caused by OE, RA or acute gouty arthritis. Arcoxia was the only COX-2 selective inhibitor licensed to treat these conditions; no other medicine in the class was licensed for use in acute gout. However, Bextra (valdecoxib) was licensed to treat not only OA and RA but also primary dysmenorrhoea. Vioxx Acute could be used for acute pain and primary dysmenorrhoea. The indications for Arcoxia all related to conditions involving arthritis and although wide in that regard, Bextra and Vioxx Acute could both be used for non-arthritic conditions. Furthermore, although Arcoxia was a COX-2 selective inhibitor, it nonetheless belonged to the wider class of non-steroidal anti-inflammatory drugs (NSAIDs) which could be used to treat inflammation and pain associated with a very wide variety of conditions.

Merck Sharp & Dohme was asked to respond in relation to the requirements of Clauses 3.2 and 7.2 of the Code.

RESPONSE

Merck Sharp & Dohme stated that the three licensed indications for Arcoxia, the symptomatic relief of OA, RA and the pain and signs of inflammation associated with acute gouty arthritis, although all affecting skeletal joints, varied greatly in their aetiology and pathology.

OA was largely a degenerative disease of joint tissue with a small inflammatory component, which caused pain and disability at the time of, or following, movement. Treatment for many patients with therapies such as Arcoxia was on an intermittent basis when symptoms required.

RA was a systemic autoimmune disease that affected a variety of organs including synovial joints. It was characterised by destructive inflammatory 'flares' followed by pain and disability as a result of the residual destruction of joint and surrounding tissues. RA was treated chronically and continuously with medicines such as Arcoxia.

Acute gouty arthritis was a crystal deposition-induced acute inflammatory joint disorder that was excruciatingly painful in the acute phase. Arcoxia had anti-inflammatory analgesic properties that were used for the acute symptomatic period; different medicines with different modes of action were used for long-term therapy.

The three indications thus comprised a broad range of medical conditions. They were widely disparate in the key areas of aetiology, pathology, symptomatology and treatment. Arcoxia was the only COX-2 selective

inhibitor with a marketing authorization covering these widely differing conditions, as no other medicine in this class was licensed for use in acute gout. For these reasons, Merck Sharp & Dohme submitted that this range of indications was indeed 'broad' and that describing the product in this manner was not inconsistent with the particulars listed in the SPC. Furthermore, this term had been used to describe this range of indications for two years, and there was no evidence, in terms of adverse comment from prescribers, other health professionals or competitor companies, that this wording was misleading.

Merck Sharp & Dohme did not agree that the claim was broader than the licensed indications for the product and thus inconsistent with the marketing authorization. It noted that the claim was not comparative. It made no assertions about the 'broadness' of the indications of other selective COX-2 inhibitors or the NSAIDs, indeed those who marketed the other medicines referred to would probably equally feel that their products were also licensed in 'a broad range of indications', given the significant number of indications noted. The strapline might also be true for those products.

The claim had been carefully worded. It did not state that any or all painful or inflammatory conditions in general were indications for the use of Arcoxia. Responsible prescribers would be expected to confirm the indication of Arcoxia before prescribing it. This claim had been in use with the current range of indications for about two years in the UK and it was also used in other countries with the same indications. The company knew of no instances where the claim had caused confusion or concern amongst prescribers, nor was it aware that the claim had resulted in any inappropriate prescribing.

Merck Sharp & Dohme stated it was not promoting indications not covered by the marketing authorization. All Merck Sharp & Dohme advertisements stated that the SPC must be referred to before the medicine was prescribed. Physicians would not prescribe a medicine based on a three page advertisement stating a 'broad range of indications' without looking to see what those indications were. Reference to the SPC was essential.

Merck Sharp & Dohme submitted that the definition of 'broad' covered OA, gout and RA, three separate clinical entities with different aetiologies as noted above. These three conditions required separate licensing authorizations. They were not simply homogenous rheumatological disorders. They were as different as if the three indications had been acute pain, dysmenorrhoea and gout. There had been no comparison with other products or use of the terms 'broader' or 'broadest'.

Merck Sharp & Dohme submitted that it was important to assess the claim in terms of the overall marketing of Arcoxia. All of the representatives promoted only the three indications for Arcoxia (OA, RA and gout). This was the message received by doctors in conjunction with the claim 'broad range of indications' and the advertisement merely served to remind them of the existence of the medicine.

Merck Sharp & Dohme noted that there was no evidence to suggest that prescribing practise, in terms of the 'broadness' of Arcoxia usage had been adversely affected. In a market research survey conducted in June 2004, 274 GPs were asked about the diagnosis of the last two patients whom they treated with Arcoxia. The results were as follows: OA 42%; gout 25%; RA 18%; lower back pain 10%; ankylosing spondylitis 1%; joint pain 1%; dysmenorrhoea 0%; and other 3%. These results reflected the perceived action of GPs and thus the message which they had received from promotional activity, including the claim in question. The vast majority of the usage was in the licensed indications. The 10% usage in lower back pain reflected the overlap and diagnostic difficulty in this area. There were no reported prescriptions for either dysmenorrhoea or acute pain, the indications which had been highlighted as problematic.

The phrase 'broad range of indications' had been used for the past two years without complaint that there was a potential for misinterpretation. The market research results quoted above confirmed that there had been no misunderstanding as a consequence of this longstanding phrase which had been used since product launch.

PANEL RULING

The Panel noted that there was nothing in the advertisement to suggest to the prescriber that Arcoxia was only licensed in OA, RA and acute gouty arthritis. The two claims 'The power to move you' and 'POWER to relieve pain and inflammation in a broad range of indications' appeared stark against the background. The Panel considered that, in the context in which it appeared, the phrase 'broad range of indications' for a COX-2 selective inhibitor might be read by some as meaning that the product could be used for more than just arthritic conditions given that other such medicines could be used for non-arthritic conditions such as acute pain of any origin and primary dysmenorrhoea. The Panel considered that in the advertisement in question the claim was misleading and inconsistent with the particulars listed in the SPC. Breaches of Clauses 3.2 and 7.2 of the Code were ruled.

Proceedings commenced 17 March 2004

Case completed 4 October 2004

ANONYMOUS v BRISTOL-MYERS SQUIBB

Conduct of representative

A woman with HIV complained anonymously about the conduct of a representative from Bristol-Myers Squibb.

The complainant stated that she was in a clinic when a woman who she thought was a doctor started to tell her about a new HIV medicine. The complainant then saw that the woman had her young daughter with her and thought that she was another patient. The complainant thought the medicine would be good for her so she asked her doctor about it. Her doctor did not want her to have it and said that this woman should not have told her about it. The complainant gave her doctor the leaflet the woman had given her.

The complainant found out from the clinic nurse the name of the woman, that she worked for Bristol-Myers Squibb and that she was not a doctor or a patient but was selling the medicine and that it was against the Code to tell patients about it. The complainant was cross and upset as the representative had asked her lots of things about herself and her illness but was pretending to be a doctor. She would not have told her private things if she had known. The complainant was surprised that staff were allowed to take their children to work with them.

The complainant's doctor had said she should write to the Authority to make sure that the representative did not keep pretending to be someone she was not.

The Panel noted that the parties' account of events differed; it was thus difficult to determine exactly what had transpired. The complainant knew that the representative had been accompanied by her daughter. Bristol-Myers Squibb had denied that its representative had talked to the patient as alleged.

The Panel noted that in cases concerning what a representative had said it usually sent the response to the complainant for comment before it made its ruling. This was not possible in this instance as the complainant was anonymous. The Panel had no option other than to rule no breach of the Code.

A woman with HIV complained anonymously about the conduct of a representative from Bristol-Myers Squibb Pharmaceuticals Limited.

COMPLAINT

The complainant stated that she was in a clinic on 6 August when a woman who she thought was a doctor started to tell her about a new HIV medicine. The complainant then saw that the woman had her young daughter with her and thought that she was another patient. The complainant thought the medicine would be good for her so she asked her doctor about it. Her doctor did not want her to have it and said that this woman should not have told her about it. The complainant gave to her doctor the leaflet the woman had given her.

The complainant found out from the clinic nurse the name of the woman, that she worked for Bristol-Myers Squibb and that she was not a doctor or a patient but was selling the medicine and that it was against the ABPI Code to tell patients about it. The complainant was cross and upset as the representative had asked her lots of things about herself and her illness but was pretending to be a doctor. The complainant would not have told her private things if she had known. The complainant was surprised that staff were allowed to take their children to work with them.

The complainant's doctor had said she should write to the Authority to make sure that the representative did not keep pretending to be someone she was not.

When writing to Bristol-Myers Squibb, the Authority asked it to respond in relation to Clauses 15.2 and 20.1 of the Code.

RESPONSE

Bristol-Myers Squibb confirmed that the representative was present in the unit in question on the day specified. She had an appointment with two doctors detailing product information and had a brief discussion with two nurses who were in uniform. The representative sat in the waiting room with her daughter and had her sales aid open while in a public area. She had a discussion with two nurses in a corridor but did not detail anyone in a public area. The representative denied any patient contact and denied having a conversation with, or giving any information or material to, a patient.

Two consultants at the unit and the clinic manager confirmed that the representative was present with her daughter. There were no HIV patients scheduled into the clinic diary on that day and no HIV patients were seen in clinic on that day by either consultant or nursing staff. HIV clinic days were Monday, Tuesday and Thursday. The representative did interview one of the doctors with the door open. All the members of staff interviewed by the representative's manager were surprised that a complaint had been made. The doctors were unclear how a patient would know how to lodge an official complaint.

Although Bristol-Myers Squibb could not confirm that the representative had any patient contact, it found this unlikely given the evidence. It also did not know if any leavepieces were given to an inappropriate person but also found this unlikely. The representative's level of training, experience and interview suggested that she would have sufficient knowledge of the Code and its implications to avoid this type of error.

Bristol-Myers Squibb noted that the complainant stated '…….started telling me about a new medicine …'. Although the company had recently launched a new protease inhibitor, Reyataz, the representative did not cover this particular brand, had not been trained on it and did not carry any Reyataz

promotional material. The products that she promoted were a number of years old and would not be considered 'new'.

Bristol-Myers Squibb therefore believed that there had been no breach of the Code as alleged.

Bristol-Myers Squibb stated that it would address the issue of the representative having her child with her as this was against company policy.

PANEL RULING

The Panel noted that the parties' account of events differed; it was thus difficult to determine exactly what had transpired at the clinic in question. The complainant knew that the representative had been accompanied by her daughter. Bristol-Myers Squibb had denied that its representative had talked to the patient as alleged.

The Panel noted that usually in cases concerning what a representative had said the response was sent to the complainant for comment before the Panel made its ruling. This was not possible in this instance as the complainant was anonymous.

The Panel had no option other than to rule no breach of the Code.

Complaint received	**16 August 2004**
Case completed	**27 August 2004**

CODE OF PRACTICE REVIEW – NOVEMBER 2004

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

1516/9/03	**Pfizer v Allergan**	**Promotion of Lumigan**	**Breaches Clauses 2 and 18.1** **Audit required by Appeal Board** **Further audit required by Appeal Board**	**Report from Panel to Appeal Board** **Report to ABPI Board**	**Page 3**
1519/9/03	**Primary Care Trust Clinical Governance Lead v Trinity**	**Practice Switch Programme**	**Breaches Clauses 2 and 9.1 Two breaches Clause 18.1** **Audit required by Appeal Board** **Further audit required by Appeal Board**	**Report from Panel to Appeal Board** **Report to ABPI Board**	**Page 6**
1559/3/04 & 1560/3/04	**Lilly v Bristol-Myers Squibb and Otsuka**	**Promotion of Abilify**	**Breach Clause 2 Five breaches Clause 3.1 Breaches Clauses 9.1 and 15.9** **Audit required by Appeal Board** **Further Audit in March 2005 required by Appeal Board**	**Report from Panel to Appeal Board**	**Page 11**
1564/3/04	Pfizer v Allergan	Alleged disparagement of Pfizer	No breach	No appeal	Page 24
1570/3/04	Janssen-Cilag/Director v Lilly	Alleged breach of undertaking	No breach	Appeal by respondent	Page 25
1572/4/04	**Novartis v Roche**	**Bondronat journal advertisements**	**Two breaches Clauses 7.2 Two breaches Clause 7.3 Two breaches Clause 7.4 Breach Clause 7.10**	**Appeal by respondent**	**Page 33**
1574/4/04	**Pfizer v AstraZeneca**	**Promotion of Crestor**	**Breach Clause 4.3 Two breaches Clause 7.2 Two breaches Clause 7.4 Two breaches Clause 7.10**	**Appeals by complainant and respondent**	**Page 42**
1579/4/04	**GlaxoSmithKline v AstraZeneca**	**Symbicort leavepiece**	**Breaches Clauses 7.2, 7.3 and 7.4**	**No appeal**	**Page 50**

1580/4/04	**Head of Primary Care Trust Prescribing Support Unit v GlaxoSmithKline**	**Avandia and Avandamet journal advertisement**	**Breaches Clauses 3.2 and 7.2**	**No appeal**	**Page 57**
1585/4/04	Novo Nordisk v Aventis Pharma	Lantus booklets	No breach	No appeal	Page 60
1587/5/04	Diabetes Specialist Nurse v Aventis Pharma	Alleged promotion of Lantus to diabetes group	No breach	No appeal	Page 63
1588/5/04 & 1589/5/04	**Primary Care Trust Lead Prescribing Support Pharmacist/Director v Sanofi-Synthelabo and Bristol-Myers Squibb**	**Plavix jounal advertisement**	**Breaches Clauses 7.2 and 7.4**	**Appeal by respondent**	**Page 65**
1590/5/04	**Primary Care Trust Director of Clinical Governance v GlaxoSmithKline**	**Rosiglitazone (Avandia and Avandamet) journal advertisement**	**Breach Clause 7.2**	**No appeal**	**Page 69**
1591/5/04	**Janssen-Cilag v Napp**	**Promotion of Transtec**	**Breaches Clauses 7.2, 7.4 and 8.1**	**No appeal**	**Page 72**
1592/5/04	**Gilead Sciences v GlaxoSmithKline**	**Epivir and Ziagen leavepiece**	**Breaches Clauses 7.2 and 7.10**	**No appeal**	**Page 76**
1594/6/04	**Roche v Novartis**	**Zometa detail aid**	**Breach Clause 3.1 Four breaches Clause 7.2 Breaches Clauses 7.3 and 7.4 Three breaches Clause 7.10**	**Appeals by complainant and respondent**	**Page 84**
1595/6/04 & 1596/6/04	**Voluntary admission by Bristol-Myers Squibb and Otsuka**	**Abilify mailing**	**Breach Clause 3.1**	**No appeal**	**Page 105**
1598/6/04	**GlaxoSmithKline Consumer Healthcare v Pfizer Consumer Healthcare**	**Nicorette Patch journal advertisement**	**Breaches Clauses 4.7 and 7.2**	**No appeal**	**Page 107**
1599/6/04	**Novartis v Roche**	**Press articles about Bondronat**	**Breach Clause 3.2 Six breaches Clause 7.2**	**No appeal**	**Page 110**
1600/6/04	**Denfleet Pharma v Novartis**	**Clozaril booklets**	**Nine breaches Clause 7.2 Eight breaches Clause 7.4**	**No appeal**	**Page 120**
1601/7/04	Primary Care Trust Medicines Management Facilitator v Pfizer	Conduct of representative	No breach	No appeal	Page 128
1605/7/04	Consultant Pharmacist v Lundbeck	Cipralex journal advertisement	No breach	No appeal	Page 130
1611/8/04	**Media/Director v Bayer**	**Promotion of Avelox**	**Breaches Clauses 7.2 and 7.4**	**No appeal**	**Page 132**
1612/8/04	**Schwarz Pharma v Stiefel**	**Promotion of Duac**	**Breaches Clauses 7.2 and 7.4**	**No appeal**	**Page 134**

1613/8/04	**Baxter Healthcare v Johnson & Johnson Wound Management**	**Promotion of Quixil**	**Breach Clause 3.2**	**No appeal**	**Page 137**
1614/8/04	**Scrutiny/Director v Merck Sharp & Dohme**	**Arcoxia journal advertisement**	**Breaches Clauses 3.2 and 7.2**	**No appeal**	**Page 139**
1621/8/04	Anonymous v Bristol-Myers Squibb	Conduct of representative	No breach	No appeal	Page 141

PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

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

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

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

It covers:

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

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

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

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