PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 52 MAY 2006

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.

Sport and leisure venues for meetings?

The supplementary information to Clause 19.1 of the Code, Meetings and Hospitality, states, *inter alia*, that venues for meetings must be appropriate and conducive to the main purpose of the meeting; lavish and deluxe venues must not be used and companies should avoid using venues that are renowned for their entertainment facilities. The impression that is created by the arrangements for any meeting must always be kept in mind. Meetings organised for groups of doctors, other health professionals and/or appropriate administrative staff which are wholly or mainly of a social or sporting nature are unacceptable.

When large numbers of delegates are to be invited to a meeting it may be impossible to hold it at a business style hotel. A conference centre within a football stadium or the like may have to be used instead. Companies organising, or sponsoring, meetings at such high profile venues should be satisfied that no other venue is large enough to accommodate the meeting and that the overall impression given by the proposed arrangements would not be unacceptable in relation to the requirements of Clause 19.1. Gratuitous use of sporting or leisure venues is unacceptable. It must be the programme that attracts delegates to a meeting, not the venue. Further, companies must ensure that no sporting events take place at the venue immediately before, during or immediately after the meeting. Venues must not be used so as to knowingly take advantage of any entertainment/sport that has been organised/subsidised by a third party.

Representatives

Clause 15.9 of the Code requires companies to prepare detailed briefing material for medical representatives on the technical aspects of each medicine which they will promote. Briefing material must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. The supplementary information to Clause 15.9 states that such briefing material consists of both the training material used to instruct the representatives about the medicine and the instructions given to them as to how the product should be promoted. Clause 15.9 makes no distinction between written and oral instructions.

Companies are reminded that the certification requirements of Clause 14 of the Code apply to briefing material prepared for representatives in accordance with Clause 15.9.

Their job titles

Companies are reminded that Clause 16.3, which states that 'Representatives must pass the appropriate ABPI representatives examination …' must be interpreted in accordance with Clause 1.6 which defines the term 'representative' as meaning a representative calling on members of the health professions and administrative staff in relation to the promotion of medicines. Thus the term 'representative' is defined by role and is wholly independent of company job title.

Public reprimand for Serono

Serono Limited has been publicly reprimanded by the ABPI Board of Management following breaches of the Code. The ABPI Board considered this was an extremely serious matter.

Full details can be found at page 3 of this issue of the Review in the report for Case AUTH/1726/6/05.

Other codes of practice

Links to both the European and national codes of practice for the promotion of medicines can be found at www.efpia.org under publications. In this regard companies are reminded that, in accordance with Clause 1.7 of the ABPI Code, they 'must comply with all applicable codes, laws and regulations to which they are subject'.

Two happy events…

Etta Logan, the Authority's Secretary, has a son, Logan, who was born in March. Etta will be on maternity leave until later this year. Peter Clift, Executive Officer, has a daughter, Eliza, who was born in February. The Authority sends its best wishes to both families.

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.

The next Code of Practice seminar dates on which places remain available are:

Monday, 4 September

Friday, 6 October

Friday, 1 December

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

For further information regarding any of the above, please contact Jean Rollingson for details (020 7930 9677 extn 4).

How to contact the Authority

Our address is:

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

www.pmcpa.org.uk

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7930 9677 extn 5).

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

Heather Simmonds: 020 7747 1438
Jane Landles: 020 7747 1415

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

Etta Logan is currently on maternity leave.

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

CASE AUTH/1726/6/05

SCHERING HEALTH CARE v SERONO

Multiple sclerosis project

Schering Health Care complained about a multiple sclerosis (MS) project sponsored by Serono. The project was described as an observation of the clinical outcome of patients treated with high dose (44mcg) interferon beta-1a (Serono's product Rebif) following cessation of treatment with lower dose interferon, defined as either 22mcg beta-1a (Rebif or Biogen's product Avonex) or 250mcg beta-1b (Schering Health Care's product Betaferon). It was being conducted on a multicentre, multinational basis with prospective patient follow-up over 2 years.

Schering Health Care alleged that the project, described by Serono as a 'Clinical Practice audit' was in fact a research study requiring assessment by a research ethics committee.

The company noted that doctors had been offered £700 to participate in the project and alleged that paying neurologists to collect data on patients switching to Rebif 44mcg was not justified by the amount of work involved and amounted to an inducement to prescribe Rebif.

Schering Health Care noted that the protocol contained several promotional statements regarding Rebif 44mcg, eg supporting the alleged 'greater benefits … compared to lower dose regimens'. The impression that the project was designed to encourage switches to Rebif 44mcg was reinforced by the statement 'Thus it seems reasonable to assume that patients who have clinically significant disease on lower therapy will benefit from dose escalation'. Schering Health Care alleged that the project amounted to disguised promotion.

Schering Health Care also disputed Serono's repeated assertion in the protocol that Betaferon 250mcg was a 'low dose' product. Betaferon could not be considered as 'low dose' in the same way as Rebif 22mcg, as the latter was only licensed for patients who could not tolerate Rebif 44mcg. There were no head-to-head comparative data of Betaferon and Rebif 44mcg. There was no evidence that 'the lower activity of Betaferon may have dose implications in some patients' as stated in the protocol. Schering Health Care alleged that this was an inaccurate and misleading comparison of Betaferon and Rebif 44mcg.

Overall, Schering Health Care alleged that Serono's activities were particularly serious and likely to bring discredit upon, and reduce confidence in, the pharmaceutical industry in breach of Clause 2 of the Code.

The Panel noted that there was a difference between clinical research and clinical audit. Clinical research created new knowledge and might form the basis of agreed guidelines and standards. Clinical audit examined practice and compared it with guidelines.

The Panel noted that the main objectives of the project entitled 'Clinical Practice Audit: Outcome of high dose interferon (IFN) therapy following dose escalation from lower dose therapy' were to determine the clinical considerations surrounding changing interferon treatment in patients failing low dose interferon (Rebif 22mcg, Avonex or Betaferon) and evaluate the clinical treatment outcome of dose escalation (treatment with Rebif 44mcg) in patients with relapsing MS who failed lower dose interferon (Rebif 22mcg, Avonex or Betaferon). In the Panel's view, the stated objectives were inconsistent with its description as a clinical audit. The project had been set up to determine clinical considerations and assess clinical outcomes, not to measure clinical practice vs any stated treatment guidelines. There was no mention of agreed guidelines in the project protocol.

The Panel considered that the project would have the effect of increasing the prescription of Rebif 44mcg. Each participating centre was invited to enrol at least 10 patients over a 12 month period. A grant of €1,000 or sterling equivalent per patient was provided to cover administrative costs. Thirty neurologists were invited to participate. In the Panel's view the project was unacceptable as it was not a bona fide audit as described and the arrangements were such that they amounted to paying doctors to prescribe Rebif 44mcg. The Panel ruled that the project constituted disguised promotion of Rebif 44mcg in breach of the Code. It followed that payments offered for participation were inappropriate and a further breach of the Code was ruled.

The Panel considered that the overall arrangements were such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. Doctors were, in effect, being paid to prescribe Rebif 44mcg. A breach of Clause 2 was ruled. The Panel also decided to report Serono to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Panel noted that the protocol repeatedly referred to Betaferon as 'low' or 'lower' dose interferon. Although Serono's product Rebif could be administered in a lower (22mcg) or a higher (44mcg) dose, Betaferon only had one licensed dose of 250mcg. In that regard the Panel considered that it was misleading to refer to Betaferon as a low or lower dose interferon. A breach of the Code was ruled.

A section of the protocol headed 'Interferon beta-1b' discussed *in vitro* data (Runkel *et al* 1998 and Antonetti *et al* 2002) which showed that the antiviral activity of Betaferon was less than that of Rebif. It was stated that this difference resulted in the licensed dose of Betaferon being equivalent to half that of Rebif. Although it was further stated that the relationship between the antiviral activity of interferons and clinical efficacy was not fully understood and that the lower activity of Betaferon might have dose implications in some patients, the Panel considered that it was nonetheless misleading to imply that Betaferon would not be as efficacious as Rebif when there had been no head-to-head

clinical studies of the two. The implication of clinical inferiority was strengthened by the repeated reference to Betaferon as a 'low' or 'lower' dose interferon. A further breach of the Code was ruled.

Upon consideration of the report made by the Panel, the Code of Practice Appeal Board expressed extreme concern about the project which in its view clearly required ethical approval.

The Appeal Board noted from Serono that ethics approval had not been required in four European countries but had been required and granted in a fifth. Advice on the need for ethics approval in the UK had been sought from a lead consultant. Within Serono the project had been given scientific approval on a corporate level. The Appeal Board was extremely concerned as to how the project achieved scientific approval, noting that the total sample size was not stated in the protocol, there was no data analysis plan, no hypothesis, no comparator and no collection of safety data. Despite the company's submission that it was designed to assess 'real life' clinical practice, the design was such that there appeared to be no valid scientific outcome. The letter inviting clinicians to participate stated that centres were invited to enrol at least 10 patients over a 12 month period. A further concern was that the study referred to Rebif 22mcg as low dose interferon treatment when according to the summary of product characteristics Rebif 22mcg was recommended for patients who could not tolerate the higher dose (Rebif 44mcg) in the view of the treating specialist. Thus such patients should not be switched to Rebif 44mcg.

The Appeal Board noted the submission that the payment of €1,000 per patient was calculated to include institutional costs. It was only paid for patients changed to Rebif 44mcg either on entry or changed within the previous three months.

The Appeal Board considered that the project showed a serious lack of understanding and was extremely concerned that doctors were in effect being paid to prescribe Rebif 44mcg. The Appeal Board was concerned that the doctors involved in the project might assume that the arrangements were acceptable and so it decided to require Serono to take steps to recover the payments as set out in Paragraph 10.3 of the Constitution and Procedure. Serono should contact each doctor to whom a payment had been supplied and request its return and explain the reasons for the request.

The Appeal Board decided to report Serono to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure.

The Appeal Board noted that it would have required Serono to undergo an audit of its procedures in accordance with Paragraph 10.4 of the Constitution and Procedure. However, in order not to delay the report to the ABPI Board, the Appeal Board decided to recommend to the Board that such an audit was carried out. The Appeal Board also decided to recommend to the Board that Serono be publicly reprimanded and be required to publish a corrective statement.

The ABPI Board considered that this was an extremely serious matter and decided that Serono should undergo an audit. In addition the Board considered that the breaches ruled by the Panel warranted the imposition of a public reprimand.

On receipt of the audit report the ABPI Board considered that Serono had made progress. It decided that the company should be audited in three or four months' time (June 2006) to ensure that the recommendations in the audit report had been implemented.

Schering Health Care Ltd complained about a multiple sclerosis (MS) audit sponsored by Serono Limited. The audit was described as an observation of the clinical outcome of patients treated with high dose (44mcg) interferon beta-1a (Serono's product Rebif) following cessation of treatment with lower dose interferon, defined as either 22mcg beta-1a (Rebif or Biogen's product Avonex) or 250mcg beta-1b (Schering Health Care's product Betaferon). It was being conducted on a multicentre, multinational basis with prospective patient follow-up over 2 years.

COMPLAINT

Schering Health Care alleged that the project was not an audit at all, but rather a research study. By the definition of clinical audit taken from the NHS Central Office for Research Ethics Committees' (COREC) website, an audit required measurement of routine clinical practice against best practice, to assess whether best practice was being followed. Anything else amounted to research. The relevant definitions were highlighted in the NHS Research and Development Forum guidance. It was a statutory requirement that all research involving NHS patients, staff or resources must be assessed by a research ethics committee. This included all observational surveillance studies.

Schering Health Care noted that the Serono audit contained no assessment against best practice, but from the objectives appeared to be hypothesis-generating ie a study. The audit was also referred to as an 'observational study', a 'study' and as 'observational surveillance' on various pages of the protocol, despite the lack of patient consent or ethics approval. Most significantly, the final page of the protocol was a form requiring clinicians to declare whether or not they wished to take part in 'the clinical study'.

Schering Health Care stated that it was also very unusual for an audit to require prospective follow-up over a 2-year treatment period or to be multinational in design – these features were much more typical of a research study. If this project was indeed an observational surveillance study rather than an audit, then ethics approval and patient informed consent should have been obtained.

Schering Health Care noted that clinicians had been offered £700 to participate in the audit; £350 for baseline assessments and another £350 for follow-up. However, little if any administration would be required, since neither patient consent nor local ethics approval was required. The information collected

was very straightforward, and did not justify the generous reimbursement being offered. The most recent advice from the British Medical Association/ Association of the British Pharmaceutical Industry (BMA/ABPI) on agreed fees for pharmaceutical company work (updated 1 July 2004) provided that completion of post-marketing surveillance forms should be charged at no more than £14.50 per form, or up to £28 for a more detailed form. Clinical trial participation should be reimbursed at no more than £193.50 per hour, it appeared highly improbable from the protocol that the baseline assessment and the follow-up assessment would require almost 4 hours' work to complete.

It appeared that paying neurologists £700 to collect data on patients switching to Rebif 44mcg from competitor beta interferons or Serono's own low dose (and lower-cost) formulation of Rebif, was not justified by the amount of work involved and therefore amounted to an inducement to prescribe Rebif 44mcg in breach of Clause 18.1 of the Code.

Schering Health Care noted that the protocol also contained several promotional statements regarding Rebif 44mcg eg supporting the alleged 'greater benefits…..compared to lower dose regimens'. The protocol therefore promoted the advantages of Rebif 44mcg over the alternative treatments from which patients would be switching, and thereby sought to encourage neurologists to switch patients to Rebif 44mcg. Furthermore, there was nothing in the protocol stating that the decision to switch therapy to Rebif 44mcg should be separate from the decision to include the patient in the audit. The impression that the audit was designed to encourage switches to Rebif 44mcg was reinforced by the statement 'Thus it seems reasonable to assume that patients who have clinically significant disease on lower therapy will benefit from dose escalation'. Schering Health Care alleged that the audit therefore amounted to disguised promotion, in breach of Clause 10.2 of the Code.

Schering Health Care also disputed Serono's repeated assertion in the protocol that Betaferon 250mcg was a 'low dose' product. Betaferon could not be considered as 'low dose' in the same way as Rebif 22mcg, as the latter was only licensed for patients who could not tolerate Rebif 44mcg. There were no head-to-head comparative data of Betaferon and Rebif 44mcg, and it was certainly not possible to draw clinical conclusions from *in vitro* bioassays, such as the Serono-sponsored study Antonetti *et al* (2002). There was no evidence at all that 'the lower activity of Betaferon may have dose implications in some patients' as stated in the protocol. Schering Health Care alleged that this was an inaccurate and misleading comparison between Betaferon and Rebif 44mcg, in breach of Clause 7.2 of the Code.

Overall, Schering Health Care alleged that Serono's activities were particularly serious and likely to bring discredit upon, and reduce confidence in, the pharmaceutical industry in breach of Clause 2 of the Code.

RESPONSE

Serono referred to intercompany correspondence and explained that in June 2005, it agreed for the sake of goodwill to cease using the term 'low dose' when referring to Betaferon in any company-generated material and gave the declaration that in the conduct of any similar type of activity, the company would be mindful of comments and would take into account the COREC guidance.

Serono stated that taking into account the requirements in all countries involved in the project, it considered that the description 'Clinical Practice audit: outcome of high dose interferon (IFN) therapy following dose escalation from lower dose therapy' was accurate. It was clear from the document describing the terms of the audit, that the products were to be used in the usual manner in accordance with routine clinical practice for MS patients and in accordance with the Rebif 44mcg marketing authorization. This was highlighted three times in the protocol. The audit thus fully complied with the definition of "non-interventional trial" of EU Directive 65/65/EEC Article 2(c). The proposed program did not require EC approval, as it fell outside the scope of the Directive.

In addition to the considerations given above, Serono stated that advice from health authorities and central ethics committees in several countries was that no ethical application was required. In the UK, unlike the rest of the EU, it was impossible to have a preliminary opinion from a multi-centre research ethics committee (MREC) before full submission. It was reasonable to assume that if the relevant authorities confirmed in writing, in 5 member states that no ethical approval was required to this observational, non-interventional project, then the same was true in the UK.

The audit had the scientific and therapeutically relevant aim of documenting the clinical considerations involved in stopping treatment in individual patients receiving either lower dose interferon as determined by the treating neurologist and to evaluate the clinical outcome of dose escalation. As indicated twice in the description of the design of the program, stopping a lower dose therapy was determined by the treating neurologists in the exercise of his professional judgment.

Serono stated that UK clinicians involved in the project considered the activity to be correctly classified as an audit.

No intervention of patients was involved in the completion of the record forms, and all information was collected on an anonymous basis. The company specified that on the audit form subjects should not be identified by their names but by their assigned patient numbers.

The time scale of 2 years was entirely acceptable in view of the time taken to evaluate changes in MS, relapses, disability etc. By way of comparison, Serono noted that the Department of Health risk sharing scheme in MS was planned to run 10 years and no interim analysis was performed before all enrolled patients were at least 2 years on treatment.

Serono refuted the alleged breach of Clause 18.1 and considered the compensation to be justifiable.

Patients were only to be treated with Rebif 44mcg within the audit if the supervising clinician decided in the exercise of his own professional judgment on clinical grounds they would benefit from this treatment. Patients transferred to Rebif 44mcg up to 3 months prior to the announcement of the audit, could also be included. Serono considered that its approach was consistent with the ABPI advice on fees for investigators. The payment was offered for the work undertaken by the neurology team when they assessed the patients at each visit (up to 6 visits in the duration of the project), and was not merely compensation for the completion of the forms. Depending on the local situation, some units chose to participate out of interest and did not require any compensation. Indeed the company offered units the option not to opt for payment and/or to donate the money to a charity of their choice.

Serono also refuted the allegations of disguised promotion and stated that the protocol was factually correct and unbiased. For example, 'greater benefits…compared to lower dose regimens' was supported by Francis *et al* (2004), and Schwid *et al* (2005). Francis *et al* concluded 'This suggests that IFN beta-1a, 44 mcg tiw sc provides the most favourable benefit-to-risk ratio of available disease-modifying products for MS'.

Regarding its description of Betaferon as a low dose product, Serono considered the sentence, 'the lower activity with Betaferon may have dose implications in some patients' was a fair and balanced comment on the findings of Antonetti *et al*. This publication contained the following statement: 'In this study, the antiviral potency of (Betaferon) was markedly lower than that of Rebif. A similar conclusion was reached in a study comparing formulated Rebif with formulated (Betaferon). This evidence implied that in clinical practice, the amount of protein required to achieve a biological response would be considerably higher with (Betaferon) than with Rebif.'

Indeed, not only was the statement based on the findings of Antonetti *et al* but the statement in the protocol, written in the conditional tense, clearly expressed a hypothesis within the framework of this observational study. There was therefore no denigration of Betaferon. Furthermore, Serono noted that Section 4.2 of the Betaferon SPC stated 'The optimal dose has not been fully clarified'.

Serono stated that it had now recruited sufficient patients into the study; recruitment was closed in the UK on 30 June 2005. Participants had been informed that enrolment of patients had ceased.

PANEL RULING

The Panel noted that there was a difference between clinical research and clinical audit. Clinical research created new knowledge and might form the basis of agreed guidelines and standards. Clinical audit examined practice and compared it with the guidelines.

The Panel noted that the project at issue was entitled 'Clinical Practice Audit: Outcome of high dose interferon (IFN) therapy following dose escalation from lower dose therapy'. The main objectives of the project were to determine the clinical considerations surrounding changing interferon treatment in patients failing low dose interferon (Rebif 22mcg, Avonex or Betaferon) and evaluate the clinical treatment outcome of dose escalation (treatment with Rebif 44mcg) in patients with relapsing MS who failed lower dose interferon (Rebif 22mcg, Avonex or Betaferon). In the Panel's view, the stated objectives of the project were thus inconsistent with its description as a clinical audit. The project had been set up to determine clinical considerations and assess clinical outcomes, not to measure clinical practice vs any stated treatment guidelines. There was no mention of agreed guidelines in the project protocol.

The Panel noted that the only requirement in the Code relating to clinical assessments and the like was Clause 10.2 which stated that such activities must not be disguised promotion.

The Panel considered that the project would have the effect of increasing the prescription of Rebif 44mcg. Each participating centre was invited to enrol at least 10 patients over a 12 month period. A grant of €1,000 or sterling equivalent per patient was provided to cover administrative costs. Thirty neurologists were invited to participate. In the Panel's view the project was unacceptable as it was not a *bona fide* audit as described and the arrangements were such that they amounted to paying doctors to prescribe Rebif 44mcg. The Panel considered that the project constituted disguised promotion of Rebif 44mcg. The Panel therefore ruled a breach of Clause 10.2 of the Code. As the project was considered to be disguised promotion it followed that payments offered for participation were inappropriate and a breach of Clause 18.1 was ruled.

The Panel considered that the overall arrangements for the project were such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. Doctors were, in effect, being paid to prescribe Rebif 44mcg. A breach of Clause 2 was ruled. The Panel also decided in this regard to report Serono to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Panel noted that the project protocol repeatedly referred to Betaferon as 'low' or 'lower' dose interferon. Although Serono's product Rebif could be administered in licensed doses of either 22mcg or 44mcg, and so in that sense had a lower and a higher dose, Betaferon only had one licensed dose of 250mcg. In that regard the Panel considered that it was misleading to refer to Betaferon as a low or lower dose interferon. A breach of Clause 7.2 was ruled.

A section of the protocol headed 'Interferon beta-1b' discussed the *in vitro* data of Runkel *et al* (1998) and Antonetti *et al* which showed that the antiviral activity of Betaferon was less than that of Rebif. It was stated that this difference resulted in the licensed dose of Betaferon being equivalent to half that of Rebif. Although it was further stated that the relationship between the antiviral activity of interferons and clinical efficacy was not fully understood and that the lower activity of Betaferon might have dose

implications in some patients, the Panel considered that it was nonetheless misleading to imply that Betaferon would not be as efficacious as Rebif when there had been no head-to-head clinical studies of the two. The implication of clinical inferiority was strengthened by the repeated reference to Betaferon as a 'low' or 'lower' dose interferon. A breach of Clause 7.2 was ruled.

COMMENTS FROM SERONO

Serono fully accepted the Panel's view that the project was not an audit. The company submitted that the project was a *bona fide* study and thus it was difficult to accept the Panel's ruling that the project constituted disguised promotion and was in breach of Clause 2. Serono fully accepted the judgement regarding the level of reimbursement. In the UK 25 patients (6 centres) had been included in the study. The study had closed and senior management had visited all 6 centres.

As a result of this case Serono had appointed a consultant medical director. An independent internal review of processes and personnel covering all aspects of medical, regulatory and safety was due to report at the end of October. Standard Operating Procedures were to be reviewed and tightened. Company staff were to be trained and senior managers were to have their job descriptions enhanced to emphasise further and ensure compliance with the Code. A new medical manager had been appointed. Serono suggested a follow up meeting with the Authority in three months in order to present new processes and examples.

APPEAL BOARD CONSIDERATION

The Appeal Board was extremely concerned about the project which in its view clearly required ethical approval. The Appeal Board noted from Serono's presentation that recruitment of patients ceased in June 2005. It further noted that the whole project had closed and that the principal investigator intended to seek retrospective ethical approval from COREC.

The Appeal Board noted from the Serono representatives that ethics approval had not been required in four european countries. It was required and granted in another. Within the UK advice on the need for ethics approval had been sought from a lead UK consultant. Within Serono the project had been given scientific approval on a corporate level. The Appeal Board was extremely concerned as to how the project achieved scientific approval noting that the total sample size was not stated in the protocol, there was no data analysis plan, no hypothesis, no comparator and no collection of safety data. Despite the company's submission that it was designed to assess 'real life' clinical practice, the design was such that there appeared to be no valid scientific outcome. The letter inviting clinicians to participate stated that centres were invited to enrol at least 10 patients over a 12 month period. A further concern was that the study referred to Rebif 22mcg tiw as low dose interferon treatment when according to the summary of product characteristics Rebif 22mcg tiw was recommended for patients who could not tolerate the higher dose (Rebif 44mcg tiw) in the view of the treating specialist. Thus such patients should not be switched to Rebif 44mcg tiw.

The Appeal Board noted the submission that the payment of **€**1,000 per patient was calculated to include institutional costs. It was only paid for patients changed to Rebif 44mcg tiw either on entry or changed within the previous three months.

The Appeal Board considered that the project showed a serious lack of understanding. The Appeal Board was extremely concerned that doctors were in effect being paid to prescribe Rebif 44mcg. The Appeal Board was concerned that the doctors involved in the project might be left with the impression that the arrangements were acceptable and so it decided to require Serono to take steps to recover the payments as set out in Paragraph 10.3 of the Constitution and Procedure. Serono should contact each doctor to whom a payment had been supplied and request its return and explain the reasons for the request.

The Appeal Board decided to report Serono to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure.

The Appeal Board noted that it would have required Serono to undergo an audit of its procedures in accordance with Paragraph 10.4 of the Constitution and Procedure. However, in order not to delay the report to the ABPI Board, the Appeal Board decided to recommend to the Board that such an audit was carried out. The Appeal Board also decided to recommend to the Board that Serono be publicly reprimanded and be required to publish a corrective statement.

ABPI BOARD OF MANAGEMENT CONSIDERATION

The ABPI Board considered that this was an extremely serious matter and decided that Serono should undergo an audit of its procedures in relation to the Code. In addition the ABPI Board considered that the breaches ruled by the Panel warranted the imposition of a public reprimand.

FURTHER CONSIDERATION BY THE ABPI BOARD OF MANAGEMENT

The ABPI Board considered the audit report and Serono's comments upon it. The ABPI Board considered that Serono had made progress. It decided that the company should be audited again in three or four months' time (June 2006) to ensure that the recommendations in the audit report had been implemented.

Complaint received	**20 June 2005**
PMCPA proceedings completed	**15 September 2005**
ABPI Board of Management consideration	**19 October 2005 and 23 February 2006**

CASES AUTH/1743/7/05 and AUTH/1752/8/05

ANONYMOUS v BOEHRINGER INGELHEIM and PFIZER

Conduct of representatives

One of those present at a meeting organised by a Boehringer Ingelheim representative complained about the representative's conduct at the meeting. A representative from Pfizer was also present. The complaint was taken up with both companies.

The complainant noted that the Boehringer Ingelheim representative had taken one general practitioner, three nurses and several others to a local restaurant one Friday night. From the start the complainant was concerned with the amount of alcohol being purchased. The complainant was also concerned about comments made by the representative which implied that those at the meeting owed him something.

The Panel noted that the parties' accounts of events differed. The complainant was concerned about the amount of alcohol that was purchased by the Boehringer Ingelheim representative. Boehringer Ingelheim stated that its representative had not bought any alcohol and Pfizer stated that its representative had not submitted any receipts. It was impossible to know where the truth lay with regard to the purchase of alcohol.

Boehringer Ingelheim submitted that a nurse had invited the other attendees. The Panel was extremely concerned that Boehringer Ingelheim had submitted differing accounts about the number of attendees and the purpose of the meeting. The receipt indicated that ten people attended, contrary to the company's original submission of eight. Boehringer Ingelheim stated that three of the attendees were administrative staff. Boehringer Ingelheim initially submitted that the meeting was to discuss stress urinary incontinence, Yentreve, Spiriva and Micardis, but later stated that the meeting was to discuss incontinence issues and practice protocol which were then to be followed up with specific practice visits to promote products. The meeting was also described as an introductory meeting between representatives and the practice staff. The position was unclear. The meeting was held in the public part of a wine bar and restaurant on a Friday evening at 7.30pm. The bill was paid at 10.20pm. There was no set agenda. The food bill for the evening was £20.47/head.

The Panel noted that the invitations had been extended by a nurse. If this meant that she had also selected the invitees then this was unacceptable; the selection of those to be invited must stand up to independent scrutiny. Three of those invited were administrative staff. The content of the meeting was unclear. Nonetheless, the Panel considered that insofar as there was a clinical content it was inappropriate for administrative staff. Although the meeting might in part have been to introduce the representative(s) to the practice staff, this should not necessitate taking the staff out for a meal. The Panel was concerned that there had been no clear educational content to the meeting and even if there had been the public part of a wine bar and restaurant on a Friday night would not have provided a suitable venue for such discussions.

The Panel considered that the meeting did not have a sufficiently clear educational content such as to justify the provision of hospitality. The venue was unsuitable and the presence of administrative staff unnecessary. A breach of the Code was ruled. Both companies accepted this ruling. The Panel considered that the representatives had not maintained a high standard of ethical conduct. Breaches of the Code were ruled. Both companies accepted that the representatives had not maintained a high standard of ethical conduct but appealed the ruling that high standards per se had not been maintained.

The Panel considered that by giving the impression of taking practice staff for a Friday night out at the pharmaceutical industry's expense, the representatives had brought discredit upon the industry. A breach of Clause 2 was ruled. Both companies appealed this ruling.

The Appeal Board noted that the parties' accounts of events differed regarding the purchase of alcohol. Despite this uncertainty, the Appeal Board was nonetheless extremely concerned about the other arrangements for the meeting. Those attending, including administrative staff, had been invited to the meeting by a nurse; the representatives had met the delegates in a bar before going on to hold the meeting in a part of a restaurant where members of the public were also present; there had been no formal agenda and at the appeal hearing both companies conceded that no promotional materials had been used; Boehringer Ingelheim had paid for the attendees' meals. With these facts alone the Appeal Board considered that it was difficult to view the overall arrangements as anything other than a Friday night out at the expense of the pharmaceutical industry. Such arrangements brought discredit upon the industry, an impression heightened by the involvement of two companies; it might appear to outsiders that such a practice was commonplace. The Appeal Board upheld the Panel's rulings of breaches of the Code including the ruling of a breach of Clause 2.

During its consideration of this case the Appeal Board was particularly concerned about Boehringer Ingelheim's standard operating procedure (SOP) about meetings which appeared to give insufficient guidance with regard to the requirements of the Code. The Appeal Board decided that Boehringer Ingelheim should be required to undergo an audit of its procedures in accordance with Paragraph 10.4 of the Constitution and Procedure.

Upon receipt of the audit report, the Appeal Board remained concerned about Boehringer Ingelheim's SOPs and decided that the company should be asked to provide copies of the new ones together with evidence documenting staff training upon them. On the basis that these were acceptable to the Authority, the Appeal Board decided that no further action would be necessary.

One of those present at an evening meeting organised by a medical representative from Boehringer Ingelheim Limited complained anonymously about the representative's conduct at the meeting. A representative from Pfizer Limited was also present.

COMPLAINT

The complainant noted that on Friday, 3 June, the representative from Boehringer Ingelheim took one general practitioner, three nurses and several others to a local restaurant. From the start the complainant was concerned with the comments made and the amount of alcohol being purchased.

The complainant alleged that at the beginning of the evening the representative asked the GP if she was drinking alcohol and when told that she was driving he insisted that she have just the one to start the night. This was even though he had been told that the doctor was driving. Throughout the evening the representative bought several more rounds of drinks resulting in some attendees being unable to drive home. The complainant stated that (s)he and others felt pressured into drinking especially when having a meal bought for them. Over the past weeks the complainant had spoken to colleagues at other practices and raised her/his concerns. (S)he was told that such practice with the representative in question was usual and that he regularly took out nurses from other practices in the area.

The complainant stated that the representative made several comments concerning the cost giving the impression that those attending the meeting must return something to him and again after talking to colleagues the complainant considered that he was abusing his position and that they should not feel indebted to him. The complainant was not interested at how much the representative could spend without a problem, nor how many other practices considered that they should take part in this activity.

The complainant noted that the representative had been back to the surgery on several occasions but was not allowed access because the complainant considered strongly that (s)he would not be bought by such a person.

When writing to Boehringer Ingelheim the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2 and 19.1 of the Code.

Case AUTH/1743/7/05

RESPONSE

Boehringer Ingelheim noted that the representative had organised a meeting to discuss stress urinary incontinence, Yentreve, Spiriva and Micardis. Eight health professionals and appropriate administrative staff were invited through one of the nurses, of whom seven (two GPs, one district nurse and two practice nurses and two administrative staff) attended. The meeting was held to one side of a restaurant. In addition, a representative from Pfizer also attended, consistent with the co-promotion of Spiriva.

The meeting started at 7.30pm and the bill was paid at 10.20pm. The receipt showed that £204.70 was spent on food for 9 people (approximately £22.75 per head). Alcohol was not listed on the receipt as the attendees bought their own drinks. The representative had confirmed that he did not buy alcohol for the attendees, and that if he had done so, it would have been claimed for.

Since 3 June 2005, the representative had spoken with members of the practice on three occasions, once within the practice. Boehringer Ingelheim had also investigated the representative's other meeting activity in order to comment on the allegation that he regularly took out nurses from other practices in the area'. The representative covered an area with 149 practices. During 2005, he held 96 meetings with attendees including nurses. Twenty-five of these were evening meetings of which only five occurred on Friday evenings at the request of the invitees.

In conclusion, Boehringer Ingelheim did not consider that the meeting was in breach of Clauses 2, 9.1, 15.2 or 19.1 and that the representative had fulfilled his obligations with respect to both the Code and Boehringer Ingelheim.

In response to a request for further information Boehringer Ingelheim stated that there had been a typographical error in its original response. Ten people attended the meeting as stated on both the restaurant receipt and the meeting form. There were nine invitees. One of the nurses invited eight other health professionals. Eight health professionals attended (two GPs, one district nurse and two practice nurses and three administrative staff). There were two company personnel; one from Boehringer Ingelheim and one from Pfizer.

Boehringer Ingelheim confirmed that it did not pay for drinks at any point during the evening; this was confirmed in the company's internal investigation. This situation represented a minority of Boehringer Ingelheim evening meetings and might be initiated at the request of the delegates, as was the case for this meeting. The Pfizer representative did not pay for the meal due to a problem with his/her credit card. This situation of one company paying for the meal was not inconsistent with a co-promotion. Boehringer Ingelheim stated that the agenda was to discuss incontinence issues and practice protocol, which were to be followed up with specific practice visits to promote products and supply educational materials; these follow-up visits were carried out over the ensuing weeks. The format of the evening was a round table discussion. The invitees were chosen by one of the practice nurses. The meeting was to introduce the representatives to the practice staff as well as to discuss incontinence issues and practice protocol. The restaurant where the meeting took place sat 40-50 people. The dining area was upstairs with a small bar area separate from the dining area. This venue was a central location near the practice. It was considered to be suitable as the booking was early in the evening and the restaurant was close to empty. All relevant conversations took place within the restaurant. The attendees met at a bar across the road. The representative joined them and escorted them across the road to the restaurant. Boehringer Ingelheim noted that the representative did not buy drinks at the first bar as this was purely a rendezvous

point. All relevant conversations took place within the restaurant. There was separation between the attendees and other diners. The venue was approximately quarter full due to the early booking and there were no other diners within the immediate vicinity.

* * * * *

On learning that the meeting had also involved a representative from Pfizer, the Authority took up the matter with that company and asked it to respond in relation to Clauses 2, 9.1, 15.2 and 19.1.

* * * * *

Case AUTH/1752/8/05

RESPONSE

Pfizer confirmed that one of its experienced medical representatives was present at the meeting in question but had since resigned from the company. From the limited information available the representative's call notes showed that he contacted two GPs and a non-prescribing health professional at the meeting on 3 June. No other attendees were mentioned. Given that the meeting was held jointly with Boehringer Ingelheim, and from the meeting's call notes, Pfizer inferred that the meeting was to discuss a range of issues including chronic obstructive pulmonary disease and Spiriva and its use in general practice.

No expense claim was made by the representative for this 'nil cost' meeting. There was no record of the representative submitting the meeting for approval, nor, under the terms of the company's standard operating procedures, unless the total cost of the meeting was £500 or more, would this have been expected. No-one else from Pfizer was involved in the meeting.

Given that no specific allegations had been made against the representative, Pfizer submitted that there could be no suggestion that his activities on the company's behalf had brought discredit upon the industry.

Pfizer submitted that there appeared to be no evidence that high standards were not maintained by the representative and therefore it considered that allegations of breaches of Clauses 2, 9.1 and 15.2 were unfounded. In addition, as Pfizer had not provided any hospitality the company denied a breach of Clause 19.1.

PANEL RULING

The Panel noted that the supplementary information to Clause 14.1 of the Code, Joint Ventures and Co-Promotion, stated that if two or more pharmaceutical companies organized a joint meeting each company should ensure that the arrangements for the meeting were acceptable. It followed, therefore, that irrespective of who paid for what, Boehringer Ingelheim and Pfizer were equally and jointly responsible for the meeting in question.

The Panel noted that the parties' accounts of events differed. The complainant was concerned about the amount of alcohol that was purchased by the representative from Boehringer Ingelheim. Boehringer Ingelheim stated that its representative had not bought any alcohol and Pfizer stated that its representative had not submitted any receipts. It was impossible to know where the truth lay with regard to the purchase of alcohol.

Boehringer Ingelheim submitted that a nurse had invited the other attendees. The Panel was extremely concerned about the differing accounts given by Boehringer Ingelheim about the number of attendees and the purpose of the meeting. The receipt, the original of which was disclosed to the Panel, indicated that ten people attended contrary to the company's original submission. Boehringer Ingelheim stated that three of these were administrative staff. Boehringer Ingelheim initially submitted that the meeting was convened to discuss stress urinary incontinence, Yentreve, Spiriva and Micardis. The company subsequently submitted that the purpose of the meeting was to discuss incontinence issues and practice protocol which were then to be followed up with specific practice visits to promote products. These follow-up visits were carried out over the ensuing weeks. The meeting was also described as an introductory meeting between representatives and the practice staff. The position was unclear. The meeting was held in the public part of a wine bar and restaurant on a Friday evening at 7.30pm. The bill was paid at 10.20pm. There was no set agenda. The food bill for the evening was £20.47/head.

The Panel noted that, *inter alia*, Clause 19.1 of the Code required meetings to have a clear educational content; the associated hospitality must be appropriate and not out of proportion to the occasion and administrative staff might be invited where the subject matter was relevant to their role. The supplementary information to Clause 19.1 stated that the impression that is created by the arrangements for any meeting must always be kept in mind.

The Panel noted that the invitations had been extended by a nurse. If this meant that she had also selected the invitees then this was unacceptable. Companies must ensure that the selection of delegates stood up to independent scrutiny. Three of those invited were administrative staff. The content of the meeting was unclear. Nonetheless, the Panel considered that insofar as there was a clinical content it was inappropriate for administrative staff. Although the meeting might in part have been convened so as to introduce the representative(s) to the practice staff, this should not necessitate taking the staff out for a meal. The Panel was concerned that there had been no clear educational content to the meeting and even if there had been the public part of a wine bar and restaurant on a Friday night from 7.30-10.20pm would not have provided a suitable venue for such discussions.

The Panel considered that the meeting did not have a sufficiently clear educational content such as to justify the provision of hospitality. The venue was unsuitable and the presence of administrative staff unnecessary. A breach of Clause 19.1 was ruled. Both

companies accepted this ruling. The Panel considered that the representatives had not maintained a high standard of ethical conduct. Breaches of Clauses 15.2 and 9.1 were ruled. Both companies accepted the ruling of a breach of Clause 15.2 of the Code but appealed the ruling of a breach of Clause 9.1.

The Panel noted that Clause 2 of the Code stated that, *inter alia*, activities associated with promotion must never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. A ruling of a breach of Clause 2 was a sign of particular censure and reserved for such circumstances. The Panel considered that by giving the impression of taking practice staff for a Friday night out at the pharmaceutical industry's expense, the representatives had brought discredit upon the industry. A breach of Clause 2 was ruled. Both companies appealed this ruling.

Case AUTH/1743/7/05

APPEAL BY BOEHRINGER INGELHEIM

Boehringer Ingelheim accepted the Panel's rulings of breaches of Clauses 15.2 and 19.1 as the evidence indicated that the meeting venue might have been inappropriate and the educational and clinical context of the meeting were not sufficiently clear. However, the company's investigation into this matter, with its representative and members of the practice concerned, indicated that several of the allegations were untrue.

Nevertheless, the description of the meeting given by the practice representative did not match that of the complainant and the restaurant receipt. Importantly, the evidence from the surgery suggested that its representative did not purchase any alcohol, that drinking was not excessive and he had definitely not been refused access to the surgery.

Boehringer Ingelheim alleged that whilst there were certainly aspects of this meeting which did not conform with the Code, it was extremely concerned that a breach of Clause 2 could be ruled on the basis of a single, anonymous complaint which could not be effectively corroborated and appeared to be untrue with regard to several of the allegations.

Against this background, Boehringer Ingelheim submitted that acceptance of this ruling would set a dangerous precedent. The evidence did not support all the allegations made and Boehringer Ingelheim could not see how these facts aligned with Clause 2 censure and as a result of this information, it appealed the rulings of breaches of Clauses 2 and 9.1.

Case AUTH/1752/8/05

APPEAL BY PFIZER

Pfizer acknowledged that according to Clause 14.1 it was jointly responsible for co-promotion activities related to the promotion of Spiriva and therefore accepted the Panel's rulings of breaches of Clauses 15.2 and 19.1 as they related to the inappropriateness of the meeting venue and unclear educational or clinical content. However, Pfizer appealed the Panel's rulings of breaches of Clauses 2 and 9.1.

Pfizer noted that the breach of Clause 2 was a result of allegedly creating the impression of 'taking practice staff for a Friday night out at the expense of the pharmaceutical industry'. Pfizer firmly submitted that the alleged impression was unreasonable to attribute to the evening, especially given the doubt (detailed below) now cast upon the isolated, anonymous, uncorroborated allegations made initially, such as an apparent payment for alcoholic beverages by the industry employees.

In addition, whilst acknowledging its co-promotion responsibilities, Pfizer denied any direct involvement of its employee in the creation of a disreputable impression, with the initial complaint clearly pertaining to the specific alleged actions of a Boehringer Ingelheim representative at the meeting on 3 June and subsequent to it.

Pfizer submitted that the restaurant receipt, testimony from the Boehringer Ingelheim representative and it understood, members of the practice (see Boehringer Ingelheim's appeal), all added to the weight of evidence refuting the claims relating to alcohol purchase by the Boehringer Ingelheim representative and the general conduct at the meeting. As it was now clear that any alcohol at the event was bought by the practice staff, it should certainly not be viewed as 'a Friday night out at the expense of the pharmaceutical industry', rather an informal discussion with refreshments not exceeding a level that the recipients would normally buy themselves. Pfizer found it difficult to see how these facts should be used to bring particular censure to either company. Pfizer submitted that despite the acknowledged presence of a Pfizer representative, his actions were not referred to in any way by the complainant and there had been no subsequent accusation of impropriety on his behalf. Pfizer submitted that it fully understood its responsibilities within the co-promotion, but as it had no managerial control over this Boehringer Ingelheim employee it did not accept that a ruling of a breach of Clause 9.1 reflected the role of the Pfizer representative or its corporate role in the case and was therefore excessively punitive.

Pfizer submitted that a ruling of Clause 2 against it as a result of the alleged behaviour of a Boehringer Ingelheim representative suggested that Pfizer should be accountable for the actions and behaviours of individual representatives of other companies, even when they were alleged to have strayed outside the governance and direction of its partnership, which it deemed unreasonable.

APPEAL BOARD RULING

The Appeal Board noted that the supplementary information to Clause 14.1 of the Code, Joint Ventures and Co-Promotion, stated that if two or more pharmaceutical companies organized a joint meeting each company should ensure that the arrangements for the meeting were acceptable. It followed, therefore, that irrespective of who paid for what, Boehringer Ingelheim and Pfizer were equally and jointly responsible for the meeting in question.

The Appeal Board noted that the parties' accounts of events differed. The complainant was concerned

about the amount of alcohol that was purchased by Boehringer Ingelheim's representative. Boehringer Ingelheim stated that its representative had not bought any alcohol; Pfizer stated that its representative had not submitted any receipts. In its appeal Pfizer submitted that the alcohol had been bought by the practice staff. At the meeting itself the Boehringer Ingelheim representative stated that each of the individuals at the meeting paid for their own drinks; however it was noted that the late evidence submitted by Boehringer Ingelheim, which detailed a discussion between the company and a senior member of the practice, stated that the alcohol was purchased by the practice. It was impossible to know where the truth lay with regard to the purchase of alcohol.

Despite the uncertainty regarding the purchase of alcohol, the Appeal Board was nonetheless extremely concerned about the other arrangements for the meeting. Those attending, including administrative staff, had been invited to the meeting by a nurse; the representatives had met the attendees in a bar before going on to hold the meeting in a part of a restaurant where members of the public were also present; there had been no formal agenda and at the appeal hearing both Boehringer Ingelheim and Pfizer conceded that no promotional materials had been used; Boehringer Ingelheim had paid for the attendees' meals. Taking these facts into consideration and irrespective of the arrangements relating to the purchase of alcohol, the Appeal Board considered that it was difficult to view the overall arrangements as anything other than a Friday night out at the expense of the pharmaceutical industry. Such arrangements brought discredit upon the pharmaceutical industry, an impression heightened by the involvement of two companies; it might appear to outsiders that such a practice was commonplace within the industry. The Appeal Board upheld the Panel's rulings of breaches of Clauses 9.1 and 2 of the Code. The appeals were unsuccessful.

During its consideration of this case the Appeal Board was particularly concerned about Boehringer Ingelheim's meeting policy SOP which appeared to give insufficient guidance with regards to the understanding of the requirements of the Code. The Appeal Board decided that Boehringer Ingelheim should be required to undergo an audit of its procedures in accordance with Paragraph 10.4 of the Constitution and Procedure.

Upon receipt of the audit report, the Appeal Board remained concerned about Boehringer Ingelheim's SOPs in particular that there had been no evidence of any amendments to them to take into account the requirements of the 2006 Code and its operation. The Appeal Board decided that Boehringer Ingelheim should be asked to provide copies of the new SOPs and evidence documenting staff training upon them. On the basis that all of the documents, particularly those relating to meetings and meeting expenses, and training upon them were acceptable to the Authority, the Appeal Board decided that no further action would be necessary.

Complaint received	**20 July 2005**
Case AUTH/1743/7/05 Undertaking received	**14 November 2005**
Case completed	**20 April 2006**
Case AUTH/1752/8/05	
Case completed	**18 November 2005**

CASE AUTH/1766/10/05

GENERAL PRACTITIONER v NAPP

OxyContin mailing

A general practitioner alleged that a bar chart in an OxyContin (prolonged release oxycodone) mailing, sent by Napp, was scientific gobbledegook. The bar chart showed, for every 100 patients treated for severe neuropathic pain, the number that would achieve > 50% pain relief with tricyclics (amitriptyline (43), OxyContin (40) and gabapentin (31)). The complainant thought the chart was meaningless because the three medicines compared (ie a tricyclic antidepressant, an opioid (OxyContin) and an anticonvulsant (gabapentin)) were used in very different ways.

The Panel noted that OxyContin was indicated, *inter alia*, for the treatment of severe pain requiring the use of a strong opioid. It would thus not be a first line treatment for severe neuropathic pain but would be used when other non-opioid treatments had failed.

The bar chart compared the results for: tricyclics, in particular amitriptyline, which was not licensed for the treatment of severe neuropathic pain; OxyContin, which could be used as a second line agent, and gabapentin, which was licensed for the treatment of neuropathic pain. Given the inclusion of gabapentin the Panel considered that some readers might assume that all three medicines could be considered as first line treatment options which was not so. The Panel did not consider that the subheading which stated that OxyContin could be used when first line treatments were no longer adequate was sufficient to negate this otherwise misleading impression. The Panel noted that it was a requirement of the Code that comparisons had to be between medicines for the same needs or intended for the same purpose. This was not the case for the bar chart in question. The Panel considered that the comparison shown was misleading as alleged. Breaches of the Code were ruled which were appealed by Napp.

The Appeal Board noted that the bar chart had been adapted from Sindrup and Jensen (1999) which had reviewed a number of papers in order to evaluate number needed to treat (NNT) for various medicines. The OxyContin data depicted had originally come from an evaluation of the clinical efficacy of oxycodone in neuropathic pain using postherpetic neuralgia as a model (Watson and Babul 1998). Patients (n=38) with pain of at least moderate intensity received either oxycodone or placebo; in 30% of patients oxycodone was added to already existing treatment with antidepressants. Sindrup and Jensen stated that because of this their calculated NNT of 2.5 (1.6-5.1) had to be judged with caution. The Appeal Board noted Napp's view that the crossover design of Watson and Babul meant that the NNT from Sindrup and Jensen might be a conservative figure.

The Appeal Board noted that OxyContin could be used as first or second line treatment for moderate to severe neuropathic pain in patients with cancer and as second line treatment for patients without cancer but with severe pain requiring use of a strong opioid. The OxyContin data in the bar chart was from a clinical model of non-malignant origin. Use of gabapentin, however, was not restricted with regard to pain intensity. Amitriptyline was not indicated for neuropathic pain although the Appeal Board acknowledged that it was commonly used for that condition. The Appeal Board was concerned that the data shown in the bar chart might represent patients with different baseline pain intensities. The mailing referred to patients with severe neuropathic pain.

The Appeal Board was also concerned that, given the difference between the licensed indications and use of amitriptyline, OxyContin and gabapentin, some readers might be misled as to when each should be used. OxyContin could only be used second line for patients without cancer. The mailing had been sent to GPs who, unless they had a particular interest in the area, might not be as familiar with the medicines used to treat severe neuropathic pain as consultant physicians.

Overall, the Appeal Board considered that, as presented, it was difficult to fully understand the basis of the data and thus its clinical significance. Insufficient detail had been given. The comparison had been presented too simplistically given the basis of the data. The Appeal Board considered that the bar chart was misleading and upheld the Panel's rulings of breaches of the Code.

A general practitioner complained about a six page, gate folded mailing (ref UK/UA-05031) for OxyContin (prolonged release oxycodone) sent by Napp Pharmaceuticals Limited. The mailing was about the use of OxyContin in the treatment of severe neuropathic pain. Page 2 featured a bar chart headed 'Increasing your treatment options in severe neuropathic pain'. The bar chart showed, for every 100 patients treated, the number that would achieve >50% pain relief with tricyclics (43), OxyContin (40) and gabapentin (31). The chart had been adapted from Sindrup and Jensen (1999).

COMPLAINT

The complainant considered that the bar chart was scientific gobbledegook; it compared the strong opioid OxyContin to medicines from completely different classes, namely tricyclics and an anticonvulsant. The complainant thought the chart was meaningless because the three kinds of medicines compared were used in very different ways.

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

RESPONSE

Napp explained that OxyContin tablets were licensed for the treatment of severe pain requiring the use of a strong opioid and thus severe neuropathic pain fell within this indication. Gabapentin was licensed for the treatment of neuropathic pain and whilst the tricyclics were unlicensed in neuropathic pain, amitriptyline in particular was commonly used in this

condition. Thus these medicines were used for the same clinical purpose and the comparison between them complied with Clause 7.3.

Napp acknowledged that, unlike tricyclics and gabapentin, opioids including OxyContin tablets were not first line treatment for non-malignant pain and had clearly emphasised this in the bullet point immediately above the visual. 'OxyContin tablets provide real results when first line treatments for severe neuropathic pain are no longer adequate'. Napp considered that this point was sufficiently prominent such as to comply with Clauses 7.2 and 7.3.

The data quoted in the mailing came from Sindrup and Jensen which evaluated the efficacy of a variety of pharmacological treatments (from different classes) for neuropathic pain. The authors explained that NNT (number needed to treat) methodology permitted clinically relevant comparison between different medicines and disorders.

Napp acknowledged that some GPs were unfamiliar with NNT analysis and so the data was presented in a simple fashion to show the number of patients out of every 100 that would achieve the endpoint for the analysis, ie greater than 50% pain relief. This was why Napp used the term 'adapted from' on the bar chart. A detailed explanation of the NNT calculation and this methodology could be found in a review by Cook and Sackett (1995). Sindrup and Jensen derived the NNT data for oxycodone from Watson and Babul (1998).

In summary, Napp considered that the comparison at issue was scientifically valid and used a widely accepted methodology which had been accepted for publication by a respected peer reviewed journal. The agents compared were all commonly used for the treatment of neuropathic pain. Napp had taken care to promote OxyContin tablets only for severe neuropathic pain in accordance with its licensed indication and had clearly emphasised its place as a second line treatment for this condition. Napp considered that the mailing complied with the Code.

PANEL RULING

The Panel noted that OxyContin was indicated, *inter alia*, for the treatment of severe pain requiring the use of a strong opioid. It would thus not be a first line treatment for severe neuropathic pain but would be used when other non-opioid treatments had failed.

The bar chart in the mailing compared the results for three medicines: tricyclics, in particular amitriptyline, which was not licensed for the treatment of severe neuropathic pain; OxyContin which could be used as a second line agent, and gabapentin which was licensed for the treatment of neuropathic pain. Given the inclusion of gabapentin the Panel considered that some readers might assume from the bar chart that all three medicines could be considered as first line treatment options which was not so. The Panel did not consider that the subheading which stated that OxyContin could be used when first line treatments were no longer adequate was sufficient to negate the otherwise misleading impression with regard to OxyContin's place in therapy. The Panel noted that Clause 7.3 of the Code stated, *inter alia*, that comparisons were only permitted in promotional material if medicines for the same needs or intended for the same purpose were compared. This was not the case for the bar chart in question. The Panel considered that the comparison shown was misleading as alleged. Breaches of Clauses 7.2 and 7.3 were ruled.

APPEAL BY NAPP

Napp noted the Panel's observation that OxyContin tablets were indicated for the treatment of severe pain requiring the use of a strong opioid, and did not dispute its submission that severe neuropathic pain fell within the scope of this indication. However the Panel appeared to have assumed that OxyContin tablets could not be used as first line therapy for severe neuropathic pain and thus the comparison with other first line treatments was misleading. Napp submitted that this assumption only applied to those patients with non-malignant neuropathic pain.

Napp acknowledged that the summary of product characteristics (SPC) for OxyContin tablets stated that strong opioids were not first line therapy for chronic non-malignant pain. However OxyContin tablets were also licensed for treatment of moderate to severe pain in patients with cancer. Around a third of cancer patients experience neuropathic pain (Davis and Walsh 2004), and use of strong opioids such as OxyContin tablets was not limited to second line in these patients.

Napp submitted that the Panel's interpretation of the place of OxyContin tablets in therapy for neuropathic pain was too limiting, since the restrictive language in the SPC did not apply to all licensed indications.

Napp noted that the Panel had concluded that the subheading, referring to the use of OxyContin tablets when first line treatments were no longer adequate, was insufficient to negate the misleading impression regarding OxyContin's place in therapy. Napp submitted that OxyContin tablets could be used either first line or second line, depending on the aetiology of the neuropathic pain. However, since the subject of the mailer was a study using non-malignant pain models, this statement was included for clarity and accuracy as required by Clause 7.2. It was positioned prominently in a large font size and a stylised bullet was used to attract the reader to it. Napp maintained that this statement clarified the appropriate use of OxyContin tablets and that it complied with Clauses 7.2 and 7.3.

Napp noted that the Panel ruling on Clause 7.3 acknowledged that comparisons were permitted between medicines for the same needs or intended for the same purpose. It also noted that amitriptyline was not licensed for the treatment of neuropathic pain. However the reference to unlicensed competitor products had been considered in previous cases for example in Case AUTH/878/5/99 where it was decided that Clause 3 (ie the requirement not to be inconsistent with the particulars in the SPC) did not apply in such cases.

Napp submitted that with regard to amitriptyline it had previously referenced the British National

Formulary (BNF) which stated under the heading 'Neuropathic and Functional Pain' that 'amitriptyline is prescribed most frequently'. Napp submitted that current IMS data indicated that around 40% of prescriptions for amitriptyline were for painful conditions. A Cochrane review of the evidence further supporting the use of tricyclics antidepressants, in particular amitriptyline, for neuropathic pain, was also provided (Saarto and Wiffen 2005). These references strongly supported the view that amitriptyline was intended for, and commonly used for, the treatment of neuropathic pain. Its use as a comparator in this mailing was therefore valid and complied with Clause 7.3.

Napp submitted that oxycodone, amitriptyline and gabapentin were not 'used in very different ways', as stated by the complainant. The inference made was that because they were from different pharmacological classes and used to treat pain, depression and epilepsy respectively that the three medicines were not also commonly used to treat neuropathic pain. As explained this was factually incorrect, and not 'scientific gobbledegook'.

In summary, Napp submitted that since OxyContin was not restricted to second line use in all types of neuropathic pain, it disputed the Panel's view that comparison with first line treatments was misleading. In any case, Napp noted it had included a prominent statement on its place in treatment of non-malignant pain immediately above the visual, to ensure clarity and compliance with Clause 7.2. In addition, Napp had compared medicines commonly used to treat the same condition as required by Clause 7.3.

COMMENTS FROM THE COMPLAINANT

The complainant made no comment upon the appeal.

APPEAL BOARD RULING

The Appeal Board noted that the bar chart showed how many patients out of 100 would achieve >50% pain relief when treated with tricyclics (amitriptyline) (43), OxyContin (40) or gabapentin (31). The bar chart had been adapted from Sindrup and Jensen which had reviewed a number of papers in order to evaluate NNTs for various medicines. The OxyContin data depicted in the bar chart had originally come from Watson and Babul (1998). Watson and Babul evaluated the clinical efficacy of oxycodone in neuropathic pain using postherpetic neuralgia as a model. Patients (n=38) with pain of at least moderate intensity received either oxycodone or placebo; in 30% of patients oxycodone was added to already existing treatment with antidepressants. Sindrup and Jensen stated that because of this their calculated NNT of 2.5 (1.6-5.1) had to be judged with caution. The Appeal Board noted Napp's view that the crossover design of Watson and Babul meant that the NNT from Sindrup and Jensen might be a conservative figure.

The Appeal Board noted that OxyContin could be used as first or second line treatment for moderate to severe neuropathic pain in patients with cancer and as second line treatment for patients without cancer but with severe pain requiring use of a strong opioid. The OxyContin data in the bar chart was from a clinical model of non-malignant origin. Use of gabapentin, however, was not restricted with regard to pain intensity. Amitriptyline was not indicated for neuropathic pain although the Appeal Board acknowledged that it was commonly used for that condition. The Appeal Board was concerned that the data shown in the bar chart might represent patients with different baseline pain intensities. The mailing referred to patients with severe neuropathic pain.

The Appeal Board was also concerned that, given the difference between the licensed indications and use of amitriptyline, OxyContin and gabapentin, some readers might be misled as to when each should be used. OxyContin could only be used second line for patients without cancer. The mailing had been sent to GPs who, unless they had a particular interest in the area, might not be as familiar with the medicines used to treat severe neuropathic pain as consultant physicians.

Overall, the Appeal Board considered that, as presented, it was difficult to fully understand the basis of the data and thus its clinical significance. Insufficient detail had been given. The comparison had been presented too simplistically given the basis of the data. The Appeal Board considered that the bar chart was misleading and upheld the Panel's rulings of breaches of Clauses 7.2 and 7.3. The appeal was unsuccessful.

Complaint received **5 October 2005**

Case completed **2 February 2006**

CASE AUTH/1767/10/05

PRIMARY CARE TRUST CHIEF PHARMACIST v MENARINI PHARMA

Nebilet patient leaflet

The chief pharmacist to a primary care trust (PCT), complained about a patient leaflet for Nebilet (nebivolol) produced by Menarini Pharma. The leaflet, headed 'Changing your atenolol prescription', stated, *inter alia*:

'A major trial involving a large number of patients in the UK and Scandinavia has recently been completed. One of the conclusions of the trial is that some patients currently being treated with atenolol as part of their medication to control blood pressure could benefit from a change in prescription.

After considering your case, I believe you could benefit from a change in medication from atenolol to Nebilet. Whilst as effective at controlling blood pressure, Nebilet works in a different way to atenolol'.

The complainant was very concerned that the leaflet implied that Nebilet was involved in the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) which was not so. This was unacceptable and misleading.

The Panel considered that readers would assume that the two paragraphs noted above were linked and thus that the major trial (ie ASCOT) had shown that some patients currently being treated with atenolol would benefit by having their prescription changed to Nebilet, which was not so. The Panel considered that the leaflet was inaccurate and misleading as alleged and ruled a breach of the Code.

The Panel was extremely concerned about the impression given by the leaflet and considered that if patients knew the true situation then their confidence in the pharmaceutical industry would be reduced. This was a serious matter. The Panel considered that, had the Authority asked Menarini to consider the requirements of Clause 2, it would have ruled a breach of that clause as a sign of particular censure. The Panel decided to report Menarini to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board noted that ASCOT showed that hypertension outcomes were more favourable with an amlodipine based regimen than an atenolol based regimen. Following the publication of the ASCOT results there were a number of articles in the lay and medical press which stated that patients should no longer be treated with atenolol and implied, or even stated, that no beta-blockers should be used. Nebilet had not been part of ASCOT. Menarini submitted that Nebilet, although a beta-blocker, had a completely different haemodynamic profile to atenolol and in that regard the two medicines could be differentiated from one another.

The Appeal Board noted that the leaflet had been sent as part of a Nebilet promotional mailing. The mailing was a response to the media coverage of ASCOT and was intended to reassure doctors that although unfavourable results had been seen with atenolol based therapy in ASCOT, not all beta-blockers were atenolol. The Appeal Board had no doubt, however, that the purpose of the mailing was to encourage doctors to switch atenolol patients to Nebilet. There was no data to support such a recommendation. The Appeal Board considered that without the data to show that Nebilet was more beneficial to patients than atenolol, in terms of outcomes as measured in ASCOT, then patient safety could potentially be at risk. The Appeal Board considered that the leaflet implied that ASCOT had shown that some patients currently treated with atenolol would benefit from a change to Nebilet. This was not so. The Appeal Board considered that this was a very serious matter and that had it been able to rule a breach of Clause 2 of the Code, it would have done so.

The Appeal Board decided that Menarini 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 noted that over 54,500 doctors had received the leaflet; there was, therefore, a large number of prescribers who would assume that there was data to support a switch from atenolol to Nebilet. The Appeal Board noted its concerns regarding issues of safety and decided that Menarini should take steps to recover the leaflet and associated mailing, asking each clinician to whom it had been sent to return it where practicable.

Upon receipt of the audit report the Code of Practice Appeal Board was concerned about Menarini's response to it and the poor impression given of the company culture. The Appeal Board decided that the company should be reaudited in September 2006.

The chief pharmacist to a primary care trust (PCT), complained about a patient leaflet (ref NEB/MJL/304/09.05) for Nebilet (nebivolol) produced by A Menarini Pharmaceuticals UK Ltd. The leaflet, headed 'Changing your atenolol prescription', stated:

'A major trial involving a large number of patients in the UK and Scandinavia has recently been completed. One of the conclusions of the trial is that some patients currently being treated with atenolol as part of their medication to control blood pressure could benefit from a change in prescription.

After considering your case, I believe you could benefit from a change in medication from atenolol to Nebilet. Whilst as effective at controlling blood pressure, Nebilet works in a different way to atenolol'.

The leaflet then listed a number of organisations which were sources of information about blood pressure and stated:

'Follow your doctor's advice carefully with regard to dosing and how to take Nebilet. It is possible that your doctor will invite you in for a check-up after changing your medication'.

It was also stated that the leaflet was provided by Menarini as a service to the medical profession and patients.

COMPLAINT

The complainant was very concerned at the implicit message contained within this patient information leaflet; Nebilet was not involved in the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) but the leaflet read as if it was. This was unacceptable and misleading and the complainant urged that action was taken against the company to ensure that these leaflets were withdrawn from use.

When writing to Menarini the Authority asked it to respond in relation to Clause 20.2 of the Code.

RESPONSE

Menarini noted that the complainant suggested that the leaflet implied that Nebilet was included in the ASCOT study. After repeated reading of this leaflet the company could not agree that there was anything in it to imply this. The leaflet clearly stated that ASCOT concluded that many patients might need a change from atenolol. It also stated that the doctor considered Nebilet to be the appropriate alternative treatment for the individual patient to whom the leaflet was given and, that while Nebilet was as effective as atenolol in controlling blood pressure (BP), it worked in a different way. Menarini therefore did not consider that this was misleading, or that it implied anything other than it stated. It was therefore factually correct.

Menarini did not consider that the leaflet was in breach of Clause 20.2 of the Code. The purpose of the leaflet was for a doctor to give it to a patient as part of the explanation for their change in medication. The leaflet had not been provided unsolicited by a pharmaceutical company to a patient but provided solely as an 'aid to change' service to doctors for use at their discretion. No influence other than usual accepted marketing practices had been employed to facilitate a change; the choice was entirely with the doctor.

The leaflet was an example of the type of material used routinely to augment the verbal explanation given to patients by doctors. As a chief pharmacist, the complainant might not be fully familiar with the use of this type of support material by GPs, and this might in part explain the misinterpretation.

Menarini explained that the mailing was sent because the company considered it important to remind doctors that 'not all beta-blockers are atenolol'. This was to try to redress the balance in the face of a flurry of press articles making sweeping statements and assuming that specific results for the atenolol-based treatment in ASCOT applied to all beta-blockers. ASCOT showed that in hypertension, outcomes were less favourable with an atenolol-based regimen than with an amlodipine/perindopril regimen. These results meant that GPs across the UK were reviewing the treatment of large numbers of patients currently treated with atenolol, a widely used first generation beta-blocker.

As a result, there was likely to be a significant reduction in atenolol use and an increase in amlodipine/perindopril. This was entirely appropriate, however, successful treatment of hypertension frequently required the use of several adjunctive therapies. The amlodipine/perindopril regime was unlikely to be sufficient to ensure that every patient attained their BP target and, in addition, large numbers would not tolerate the treatment (in ASCOT 25% patients stopped treatment due to adverse events).

Therefore, for reasons of effectiveness or tolerability, a variety of alternative and adjunctive treatments (angiotensin receptor-blockers, third generation beta-blockers, etc.) would be used to treat some patients. As Nebilet was an established third generation beta-blocker with characteristics very different from atenolol, and was significantly less expensive than angiotensin receptor-blockers, it was an appropriate alternative that GPs would select for some hypertensive patients.

PANEL RULING

The Panel noted the wording of the leaflet and considered that readers would assume that the first two paragraphs were linked. The Panel thus considered that readers would assume that the major trial (ie ASCOT) had shown that some patients currently being treated with atenolol would benefit by having their prescription changed to Nebilet, which was not so. The Panel considered that the leaflet was inaccurate and misleading as alleged and ruled a breach of Clause 20.2 of the Code.

The Panel was extremely concerned about the impression given by the leaflet. The Panel considered that if patients knew the true situation then their confidence in the pharmaceutical industry would be reduced. This was a serious matter. The Panel considered that, had the Authority asked Menarini to consider the requirements of Clause 2, it would have ruled a breach of that clause as a sign of particular censure. The Panel decided to report Menarini to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

COMMENTS FROM MENARINI

Menarini was very disappointed that the Panel had ruled a breach of Clause 20.2 of the Code and noted the Panel did not dispute that the leaflet was factually correct. A breach was ruled on the basis that the Panel considered the leaflet text to be potentially misleading. Menarini disagreed; it was not its intention to mislead in any way. The company had, however, accepted the Panel's ruling and already acted to remove from use the small remaining number of leaflets.

Menarini submitted that the leaflet was included within a single mailing that was sent to approximately 50,000 UK general practitioners and selected hospital specialists in September 2005. At the same time a small number of leaflets was supplied to each representative and a small number had also been sent directly to GPs who had requested additional copies from the medical information department. Menarini stated that it would remove the small quantity of leaflets left in its marketing store and had already recalled any residual leaflets held by its representatives.

Menarini's disappointment at the Panel's ruling on Clause 20.2 was overshadowed by its concern at the Panel's comments about Clause 2. Although the company understood that it had not been ruled in breach of Clause 2, it regarded the reference by the Panel as very serious. As a member of the ABPI, the company considered that Clause 2 should be referred

to when there had been a major breach of the Code such as substantive factual inaccuracy, a repeat offence or intentional unethical behaviour that might adversely affect patient care or public confidence in the pharmaceutical industry. Menarini considered that the Panel's reference to Clause 2 was disproportionate in this case.

Menarini considered that any further penalty beyond that already associated with the ruling of a breach of Clause 20.2 would be inappropriate, considering the level of potential concern caused by misinterpretation of this leaflet. Comparison of this case with previous cases which the Panel had referred to the Appeal Board indicated no further action should be taken.

Menarini noted that the factually accurate leaflet was for use by a doctor where that doctor had already reviewed the patient's atenolol treatment and decided that Nebilet was an appropriate alternative. Should any recipient of the leaflet have misinterpreted the text it would not affect the treatment they received.

Menarini submitted that as a result of the ASCOT, many hundreds of thousands of hypertensive patients currently receiving atenolol would have their treatment reviewed; most would be assessed for the use of amlodipine/perindopril, the alternative regime used in ASCOT. This was entirely appropriate but, as with most antihypertensive treatments, the amlodipine/perindopril regimen alone was unlikely to ensure every patient attained their BP target (in ASCOT approximately half the patients did not reach target BP). In addition, a significant number would not tolerate the treatment (in ASCOT approximately a quarter of patients stopped treatment due to adverse events). Therefore, for reasons of effectiveness or tolerability, a variety of alternative and adjunctive treatments (angiotensin II receptor blockers, third generation beta-blockers, etc.) would be used to treat a significant number of reviewed patients. Nebilet was an established third generation, beta-blocker with characteristics very different from atenolol, and was an appropriate and effective alternative that GPs would select for some hypertensive patients that had been reviewed. GPs concerned about reactions from their primary care trust to the costs of the change from generic atenolol might have also noted that Nebilet was significantly less expensive than angiotensin II receptor blockers and indeed less than amlodipine/perindopril treatment.

Menarini submitted the leaflet 'Changing your atenolol prescription' was intended solely to assist doctors explain a change in medication to those patients where Nebilet had been assessed as the appropriate alternative to atenolol. Menarini accepted the Panel's opinion that the text on this leaflet could be misinterpreted, in breach of Clause 20.2, but this was unintentional. The Panel's reference to further sanctions was an overreaction and greatly out of proportion to any potential misunderstanding caused.

APPEAL BOARD CONSIDERATION

The Appeal Board noted that ASCOT showed that hypertension outcomes were more favourable with the amlodipine based regimen (adding perindopril when required) than the atenolol based regimen (adding bendroflumethiazide when required). Following the publication of the ASCOT results there were a number of articles in the lay and medical press which stated that patients should no longer be treated with atenolol and implied, or even stated, that no beta-blockers should be used. Nebilet had not been part of ASCOT. The Menarini representatives submitted that Nebilet, although beta-blocker, had a completely different haemodynamic profile to atenolol and in that regard the two medicines could be differentiated from one another.

The Appeal Board noted that the leaflet had been sent as part of a promotional mailing for Nebilet, and thus considered the leaflet in the context of the mailing. The mailing was a response to the media coverage of ASCOT and was intended to reassure doctors that although unfavourable results had been seen with atenolol based therapy in ASCOT, not all beta-blockers were atenolol. The Appeal Board had no doubt, however, that the purpose of the mailing was to encourage doctors to switch atenolol patients to Nebilet. There was no data to support such a recommendation. The Appeal Board considered that without the data to show that Nebilet was more beneficial to patients than atenolol, in terms of outcomes as measured in ASCOT, then patient safety could potentially be at risk. The Appeal Board considered that the leaflet implied that ASCOT had shown that some patients currently treated with atenolol would benefit from a change to Nebilet. This was not so. The Appeal Board considered that this was a very serious matter and that had it been able to rule a breach of Clause 2 of the Code, with regard to the leaflet, it would have done so.

The Appeal Board decided that Menarini 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 noted that over 54,500 doctors had received the leaflet as part of the mailing. There was, therefore, a large number of prescribers who would assume that there was data to support a switch from atenolol to Nebilet. The Appeal Board noted its concerns regarding issues of safety and decided to require Menarini to take steps to recover the leaflet and associated mailing, as set out in Paragraph 10.3 of the Constitution and Procedure, by writing to each clinician to whom it had been sent to request, where practicable, its return. That letter should be provided to the Authority for comment prior to it being sent.

FURTHER CONSIDERATION BY THE APPEAL BOARD

Upon receipt of the audit report the Code of Practice Appeal Board was concerned about Menarini's response to the audit report and the poor impression it gave of the company culture. The Appeal Board decided that the company should be reaudited in September 2006.

Complaint received **5 October 2005**

Undertaking received **22 November 2005**

GENERAL PRACTICE SURGERY PHARMACIST v SANOFI-AVENTIS and BRISTOL-MYERS SQUIBB

Plavix mailing

A pharmacist at a general practice surgery complained about a Plavix (clopidrogrel) mailing sent jointly by Sanofi-Aventis and Bristol-Myers Squibb. The mailing, *inter alia*, featured rough sketches of nine Plavix advertisements which had been chosen as finalists in a general practitioner competition run in a previous mailing. The complainant was concerned that two of the advertisements promoted Plavix for primary prevention, for which it was not licensed. The complainant noted that a third advertisement referred to the use of Plavix in stroke; the claim 'Is it time to change the management of stroke?' was based upon the CAPRIE study (clopidrogel v aspirin in patients at risk of ischaemic events) which showed no significant benefits for stroke.

The Panel considered that two of the advertisements implied that Plavix could be used for primary prevention, an indication for which it was not licensed. The first featured the claim 'Better early than late' and the second referred to Framingham data which included primary prevention data. Both advertisements were thus considered to be misleading and breaches of the Code were ruled which were not appealed by the respondents.

With regard to the third advertisement the Panel considered the claim 'Is it time to change the management of stroke?' implied that Plavix had a beneficial effect on stroke alone. Plavix was licensed to treat those patients who had a myocardial infarction (MI), ischaemic stroke or established peripheral arterial disease (PAD). The advantages for Plavix v aspirin, as shown in CAPRIE, related to the composite outcome of MI, ischaemic stroke and vascular death in this combined patient group. The CAPRIE study was not powered to detect a realistic treatment effect in any of the three clinical subgroups.

The Panel considered that the claim implied that using Plavix in preference to other agents would improve the management of stroke. With regard to aspirin the subgroup data for CAPRIE showed no statistically significant difference (p= 0.26). The Panel considered the claim implied a benefit in stroke alone for which the product was not licensed. A breach of the Code was ruled which was appealed by the respondents.

The Appeal Board noted that Plavix was indicated for the prevention of atherothrombotic events in patients suffering from ischaemic stroke (from 7 days until less than 6 months). The advertisement at issue depicted a man in a wheelchair ie someone who might have already had a stroke and thus could be prescribed Plavix for secondary prevention. The Appeal Board disagreed with the Panel's view that the advertisement implied that using Plavix in preference to other agents would improve the management of stroke, it merely promoted Plavix as an option for secondary prevention. The Appeal Board considered that the claim 'Is it time to change the management of stroke?' was within the product licence for Plavix and thus not misleading on this point; no breach of the Code was ruled. The appeal on this point was successful.

The complainant alleged that overall the mailing was unprofessional; the companies had used a competition to further claims which they knew were outside the marketing authorization for Plavix.

The Panel did not consider that the circumstances were such as to rule a breach of the Code with regard to maintaining high standards. Neither did the Panel consider that a ruling of a breach of Clause 2 of the Code was warranted. The complainant appealed these rulings.

Upon appeal the Appeal Board noted that two of the nine advertisements had been ruled in breach of the Code. The finalists had not been made to comply with the Code as promised. High standards had not been maintained and a breach of the Code was ruled. However the Appeal Board upheld the Panel's ruling of no breach of Clause 2 of the Code.

A pharmacist at a general practice surgery complained about a mailing (ref PLA-05/157) for Plavix (clopidogrel) sent by Sanofi-Aventis and Bristol-Myers Squibb Pharmaceuticals Limited. Plavix was promoted by the two companies through a co-promotional joint venture agreement.

The mailing consisted of a six page, gatefolded brochure. The first page was headed 'Think of a vascular disease patient who concerns you. Now find them inside!' Page 2 described a competition the companies had established for general practitioners which challenged them to create an advertisement showing patients who should be taking Plavix and why they would benefit. Page 3 showed the nine finalists (labelled A-I). GPs were invited to pick a winner.

Plavix was indicated for the prevention of atherothrombotic events in patients suffering from myocardial infarction (MI) (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than six months) or established peripheral arterial disease (PAD). It was also indicated for the prevention of atherothrombotic events in patients suffering from non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave MI) in combination with acetylsalicylic acid.

COMPLAINT

The complainant stated that of the nine finalists he had grave concerns about the ethics behind at least three of them, B, C, and H.

The complainant alleged that item B, which showed a man with open arms and the caption 'Better early than late', implied primary prevention and Plavix was not licensed for primary prevention.

Item C showed a man in a wheelchair with a clock and the claim 'Is it time to change the management of

stroke?' The complainant alleged that the claim was based upon the CAPRIE study (clopidogrel v aspirin in patients at risk of ischaemic events) which showed no significant benefits for stroke.

The complainant alleged that item H, which showed a man smoking a cigarette driving a train named 'Framingham' and the caption 'Stop the runaway in its tracks', implied primary prevention as Framingham calculations were not valid in secondary prevention populations.

Overall, the complainant found the mailing to be wholly unprofessional as it allowed potential advertisements to be published when they were known by the companies to be outside the existing marketing authorization. More importantly, it was disheartening that Sanofi-Aventis and Bristol-Myers Squibb considered it appropriate to hide behind a competition as a means to distribute advertisements that encouraged use of their product outside its licensed indications.

When writing to Sanofi-Aventis and Bristol-Myers Squibb the Authority asked them to respond in relation to the requirements of Clauses 2, 7.2 and 9.1 of the Code.

RESPONSE

Sanofi-Aventis and Bristol-Myers Squibb responded jointly and explained that in March 2005 an initial Plavix mailing (ref PLA 04/317) was sent to GPs detailing the use of Plavix in the secondary prevention of atherothrombotic events and offering recipients an opportunity to design an advertisement for the product. It was stated clearly that entries would be made Code compliant by the advertising agency. The prize, which had no monetary value apart from expenses incurred, was to be a visit to the advertising agency to see the advertisement being created.

The mailing in question was sent in September 2005 as a follow up to the original. Once again the mailing detailed the use of Plavix in secondary prevention of vascular events referencing the registration study, CAPRIE, referred to in Section 5.1 of the Plavix summary of product characteristics (SPC).

There were numerous references to the use of Plavix in the secondary prevention of atherothrombotic events in this mailing. The bottom of the page with the finalist sketches featured the Plavix logo below which was the statement 'delivers significant protection above and beyond aspirin in the secondary prevention of atherothrombotic events'. Page 2 summarised the results of the CAPRIE study in two paragraphs and clearly positioned Plavix within its licensed indication of secondary prevention after MI, stroke or established PAD. In addition, the bullet points on the right hand side of page 2 reminded readers about the scope of the competition, highlighting in the fourth bullet point that Plavix was for the prevention of further atherothrombotic events. Thus the context of the entire item was secondary prevention, consistent with the SPC.

With regard to item B, the companies submitted that the Plavix SPC supported the caption 'Better early than late', as Plavix was licensed for patients who had had an MI (from a few days until less than 35 days) and ischaemic stroke (from 7 days until less than 6 months). In both cases, the very specific time restrictions for starting treatment, based on the entry criteria to the CAPRIE study, were incontrovertibly early after the event rather than late. There was no suggestion of primary prevention and the wording was consistent with the marketing authorization. The companies therefore submitted that the caption did not mislead, was consistent with the SPC and not in breach of Clause 7.2.

With regard to item C 'Is it time to change the management of stroke?' the companies noted that Plavix was licensed for patients suffering from ischaemic stroke, MI or established PAD. Plavix might therefore form part of the management of a stroke patient instead of, for instance, aspirin (the comparator agent in the CAPRIE study) and was entirely consistent with its marketing authorization. Since stroke was one of the licensed indications for Plavix, the companies refuted the alleged breach of Clause 7.2 as the item accurately reflected the SPC and did not mislead.

Finally, with regard to the runaway train (item H) the companies noted that when the Framingham heart study started in 1948 it excluded participants with existing cardiovascular disease. However, over the years two further generations had been added to the original cohort and the design had been updated to answer contemporary questions including trends in events following Q-wave MI ie quite specifically, secondary prevention. D'Agostino (2000) confirmed this wider focus and gave a health risk appraisal function for subsequent coronary heart disease (CHD) events (ie people with a history of CHD or ischaemic stroke, a secondary prevention population). Therefore, in keeping with the requirements of Clause 7.2, this item was based on the most up-to-date evaluations of the Framingham data and was not in breach of the Code.

Sanofi-Aventis and Bristol-Myers Squibb submitted that they had demonstrated that the individual finalists' sketches and captions were not in breach of Clause 7.2. The companies reaffirmed their strong view that the mailing was consistent and compliant with the Code. The mailing did not discredit the industry in any way and therefore was not in breach of Clause 2; it was accurate, up to date and not misleading in accordance with Clause 7.2; and high standards had been maintained in the mailing in question, in the preceding mailing and in the conception and organisation of the competition and therefore Clause 9.1 had not been breached.

PANEL RULING

The Panel considered that the claims made in each of the nine advertisements shown in the mailing must be capable of standing alone as regard accuracy etc. In general claims should not be qualified by the use of footnotes and the like. In the Panel's view the claims would be read in the context of possible separate advertisements and would not be read in the context of the mailing as a whole. The Panel considered that

the format and layout of the mailing was such that the reader's eye would be drawn to the nine advertisements which appeared on the central page of three pages when the mailing was extended. Details of the licensed indications for Plavix, and of the CAPRIE study, appeared in the bottom left hand corner of the far left hand page. In the Panel's view this was likely to be missed by most readers who would jump straight to the nine advertisements and the far right hand page which offered them the chance to vote for a winner and request a free ear thermometer.

The Panel considered each item in turn.

The Panel considered that in item B the claim 'Better early than late' implied that Plavix could be used for primary prevention as alleged. Plavix was not so licensed. The claim was misleading in breach of Clause 7.2 of the Code. This ruling was accepted.

The Panel considered the claim 'Is it time to change the management of stroke?' in item C implied that Plavix had a beneficial effect on stroke alone. Plavix was licensed to treat those patients who had a MI, ischaemic stroke or established PAD. The advantages for Plavix v aspirin, as shown in the CAPRIE study, related to the composite outcome of MI, ischaemic stroke and vascular death in this combined patient group. The CAPRIE study was not powered to detect a realistic treatment effect in any of the three clinical subgroups.

The Panel considered that the claim implied that using Plavix in preference to other agents would improve the management of stroke. With regard to aspirin the subgroup data for CAPRIE showed no statistically significant difference (p= 0.26). The Panel considered the claim implied a benefit in stroke alone for which the product was not licensed. Thus the material was misleading and a breach of Clause 7.2 of the Code was ruled. The respondents appealed this ruling.

Turning to item H, the Panel considered that the claim 'Stop the runaway in its tracks' in conjunction with 'Framingham' on the side of the train implied that the Framingham data was relevant to the use of Plavix. The Panel noted the submission that the focus of the Framingham study had widened to include secondary prevention data. Nevertheless the Framingham data still included primary prevention data which was not a licensed indication for Plavix. The Panel considered that the item was thus misleading and ruled a breach of Clause 7.2 of the Code. This ruling was accepted.

The Panel did not consider that the circumstances justified a ruling of Clause 9.1 with regard to maintaining high standards. The Panel did not consider that a ruling of a breach of Clause 2 was warranted as this was used as a sign of particular censure. The complainant appealed these rulings.

APPEAL BY SANOFI-AVENTIS AND BRISTOL-MYERS SQUIBB

Sanofi-Aventis and Bristol-Myers Squibb jointly appealed the ruling of a breach of Clause 7.2 with regard to item C of the mailing which featured the claim 'Is it time to change the management of stroke?'.

The companies submitted that the Panel had correctly stated the licensed indications for Plavix listed in Section 4.1 of the SPC, which included ischaemic stroke. The companies therefore disagreed with the ruling 'The Panel considered the claim implied a benefit in stroke alone for which the product was not licensed'. The product was licensed for the treatment of stroke, alone.

The companies submitted that ischaemic stroke was a stand-alone diagnosis in Section 4.1 of the SPC and was not part of a symptom complex or composite. This was based on the entry criteria to the CAPRIE trial. Each patient entered into the trial only had to have **one** of the qualifying conditions, including ischaemic stroke. However, the endpoint of the trial was a composite, and this could cause confusion. This distinction between the entry criteria (input) and endpoint (output) in CAPRIE was absolutely critical as the licence was based on these parameters. CAPRIE was a comparison of Plavix v aspirin, although this was not the subject of the claim in question which made no mention or implication of a comparator, only 'Is it time to change the management of stroke?'. Further the trial was powered to detect a difference in the composite endpoint (output) regardless of qualifying condition (input): it was not powered to detect differences in the subgroups of patients entered by qualifying condition and this was reflected in Section 5.1 of the SPC: '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 thus submitted that the licence for Plavix reflected the fact that the medicine reduced further atherothrombotic events in patients who had had an MI **or** a stroke **or** who had PAD. In fact, CAPRIE demonstrated statistical significance for Plavix over and above aspirin, which was also efficacious in these conditions. Therefore, the companies refuted the Panel's ruling that the claim 'Is it time to change the management of stroke?' implied a benefit in stroke alone for which the product was not licensed and was misleading in breach of Clause 7.2.

COMMENTS FROM THE COMPLAINANT

The complainant disagreed that the claim 'Is it time to change the management of stroke?' made no mention or implication of a comparator. Current treatment of acute stroke assured future prevention against recurrent events by, *inter alia*, the use of the antiplatelet aspirin. The claim at issue implied that Plavix should be used as the antiplatelet treatment choice and not aspirin; the evidence base for this assertion was the CAPRIE study. The defence of this assertion was very similar to a previous case (Cases AUTH/1588/5/04 and AUTH/1589/5/04) in which a breach of the Code was ruled because the evidence did not support the use of Plavix over aspirin in stroke. This was based upon the fact that CAPRIE failed to show a statistically significant advantage for Plavix over aspirin in patients who were recruited to the trial with a history of MI or stroke as separate subgroups. The overall outcome of the study, which was a composite outcome, was significant.

The complainant noted that the respondents had again stated that CAPRIE was not powered to assess efficacy in the subgroups, however, as noted in Cases AUTH/1588/5/04 and AUTH/1589/5/04, a test of heterogeneity suggested that the benefits might not be identical across the three groups recruited to the trial. In addition the subgroups were defined at the beginning of the study and were discussed at length throughout the paper.

The complainant alleged that item C was thus misleading.

APPEAL BOARD RULING

The Appeal Board noted that Section 4.1 of the Plavix SPC stated that 'Clopidogrel is indicated for the prevention of atherothrombotic events in: Patients suffering from … ischaemic stroke (from 7 days until less than 6 months) …'.

The Appeal Board noted that item C depicted a man in a wheelchair ie someone who might have already had a stroke and thus could be prescribed Plavix for secondary prevention. The Appeal Board disagreed with the Panel's view that item C implied that using Plavix rather than other agents, for example aspirin, would improve the management of stroke. The Appeal Board considered that item C merely promoted Plavix as an option for secondary prevention. The Appeal Board considered that the claim 'Is it time to change the management of stroke?' was within the product licence for Plavix and thus not misleading on this point; no breach of Clause 7.2 was ruled. The appeal on this point was successful.

APPEAL BY COMPLAINANT

The complainant appealed the Panel's ruling of no breach of Clauses 2 and 9.1. The complainant noted that Clause 9.1 stated 'High standards must be maintained at all times' and alleged that the actions of Sanofi-Aventis and Bristol-Myers Squibb had been far from high in their decision to distribute a menu of advertisements that had been deemed as misleading by the Panel.

The materials were subject to checking before being sent and the complainant felt very strongly that the mailing should have been revised at this point to ensure that the competition was operated within the bounds of the marketing authorization. The complainant alleged that the ruling of a breach of Clause 7.2 demonstrated that these checks were lacking; it appeared that the companies considered it acceptable to promote their product outside its licence in the guise of a competition. A breach of Clause 9.1 should be ruled.

The complainant noted that although his complaint had been made under the 2003 edition of the Code the 2006 Code gave additional clarity with regard to Clause 2 stating that one of the reasons to rule a breach of it was when the conduct of company employees/agents fell short of competent care. The complainant stated that if he could use this supplementary information as a guide then it appeared that those responsible for drawing up the mailing and checking it had failed to show competent care in their duties. However, if the 2006 Code could not be used until January 2006 then it would be difficult to rule a breach of Clause 2 in light of the fact that the industry had not widely been brought into disrepute by the distribution of this mailing.

In response to being sent guidance in relation to rulings of Clause 2 as published in the November 2003 Code of Practice Review the complainant further noted that the Panel ruled a breach of Clause 7.2 because the mailing was considered to be misleading in that it promoted Plavix outside its current licence. This finding was based upon the fact that each of the nine winning advertisements should be able to stand alone with regard to accuracy and since item C was based upon CAPRIE the claim made for stroke patients and those in primary prevention could not be substantiated.

The complainant noted with regard to Clause 2 that the guidance in the November 2003 Code of Practice Review referred to promotion prior to the grant of a marketing authorization, conduct short of competent care and multiple/cumulative breaches. All of these applied in this case.

The complainant noted that in Cases AUTH/1588/5/04 and AUTH/1589/5/04, a breach of the Code was ruled in very similar circumstances to those now at issue, ie the promotion of Plavix in stroke. Once again Plavix was being promoted in areas where its use could not be substantiated by the evidence.

The complainant was amazed that the nine finalists of the competition in question had been chosen without considering that they should at least promote Plavix within its licence. Especially as the mailing was subject to checking before it was mailed.

The complainant alleged that the above demonstrated promotion of a product outside its licence, incompetent conduct in allowing the mailing to be distributed and cumulative breaches applicable to the same medicine with very similar unsubstantiated claims being made, therefore breaches of Clauses 2 and 9.1 should be ruled.

COMMENTS FROM SANOFI-AVENTIS AND BRISTOL-MYERS SQUIBB

Sanofi-Aventis and Bristol-Myers Squibb noted that the complainant alleged that high standards had not been maintained and stated: 'The ruling of a breach of Clause 7.2 demonstrated that these checks [prior to sending out the mailing] were lacking'. The companies alleged that this was wholly inaccurate. The mailing was certified by both companies as required by Clause 14 of the Code.

The companies stressed that they held the principles and practice of the Code in the highest regard and would never deliberately set out to mislead or promote their products outside their marketing authorization as implied. On the contrary, as previously stated the entire competition was in the context of secondary prevention of atherothrombotic events as evidenced particularly by the instructions to potential participants which highlighted that Plavix was for the prevention of **further** atherothrombotic

events. This fact was noted by the Panel in its ruling as follows: 'Details of the licensed indications for Plavix, and of the CAPRIE study, appeared in the bottom left hand corner of the far left hand page [of a three page spread]'.

The companies disagreed with the Panel that readers would jump straight to the nine advertisements in the central page and then to the right hand page, since the standard method of reading was from left to right and the materials were prepared on this basis.

The companies submitted that the thumbnail sketches of the finalists shown in the mailing were not claims nor complete advertisements, and as such they did not require prescribing information, references, a generic name etc. In addition, all of these thumbnails would necessarily be regarded in the context of the encompassing text and graphics. The piece as a whole was consistent with the marketing authorization. The context of the entire item was secondary prevention, and the companies agreed with the Panel ruling that there was no breach of Clause 9.1.

Sanofi-Aventis and Bristol-Myers Squibb noted that the complainant had stated that a breach of the Code was ruled in very similar circumstances to those now at issue, ie the promotion of Plavix in stroke where its use could not be substantiated by the evidence (Cases AUTH/1588/5/04 and AUTH/1589/5/04).

The companies submitted that the appeal of the no breach of Clause 2 appeared to be based at least in part on an entirely new complaint, of cumulative breaches, based on a previous, unrelated, complaint. The companies understood that new complaints/new grounds for appeal would not normally be accepted at this stage of the proceedings.

The companies noted that they had been advised verbally by the Authority that it had not considered this additional letter to be a new complaint about a breach of undertaking. Notwithstanding this, the companies confirmed that following Cases AUTH/1588/5/04 and AUTH/1589/5/04 they had undertaken to qualify claims substantiated by CAPRIE in their advertising materials with a further statement highlighting both the qualifying conditions in the population being studied and the composite endpoint, for example 'CAPRIE was a study of 19,185 patients with atherothrombosis as manifested by recent MI, ischaemic stroke or PVD with a combined endpoint of MI, ischaemic stroke and vascular death'. This statement therefore duly appeared on the left hand page of the item in question as noted by the Panel in its ruling.

The companies agreed with the Panel's ruling that the mailing did not warrant the particular censure of a ruling of a breach of Clause 2, and agreed with the complainant's original sentiment that 'it would be difficult to rule a breach of Clause 2 in light of the fact that the industry has not widely been brought into disrepute by the distribution of this mailing'.

The companies reiterated that the Plavix licence for ischaemic stroke was a stand-alone diagnosis in Section 4.1 of the SPC and not part of a symptom complex or composite. This was based on the entry criteria to CAPRIE. Each patient entered into the trial only had to have **one** of the qualifying conditions, including ischaemic stroke. However, the endpoint of the trial was a composite, and this could cause confusion.

The companies submitted that this distinction between the entry criteria (input) and endpoint (output) in CAPRIE was absolutely critical as the licence was based on these parameters. CAPRIE was a comparison of Plavix v aspirin, although this was clearly not the subject of the claim 'Is it time to change the management of stroke?' used in item C. The Panel had ruled a breach of Clause 7.2 because the claim implied a benefit in stroke alone for which the Panel believed this product was not licensed and was therefore misleading and in breach of Clause 7.2.

The companies noted that the complainant also alleged that Plavix was being promoted in stroke where its use could not be substantiated by the evidence.

Plavix was granted a marketing authorization through the centralised procedure based on quality, efficacy and safety. The companies provided detailed abstracts from the EPAR (European Public Assessment Report) and from the Scientific Discussion by the Committee for Proprietary Medicinal Products (CPMP).

The companies submitted that they had demonstrated that Plavix was licensed for stroke and that its marketing authorization was granted based on the efficacy and safety of Plavix v aspirin in CAPRIE and also on the superiority of Plavix over a putative placebo (as documented in the Scientific Discussion) specifically for the ischaemic stroke subgroup. Therefore it was not misleading to suggest that Plavix had a benefit in stroke ('Is it time to change the management of stroke?'), and thus it was not a breach of Clause 7.2 as alleged.

The companies submitted that further clinical support for the benefits of Plavix in stroke was given by the Royal College of Physicians' National Clinical Guidelines for Stroke, Second edition, Prepared by the Intercollegiate Stroke Working Party, June 2004.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant noted the confusion about which rulings were being appealed. The complainant noted that guidance published in the November 2003 Code of Practice Review had allowed him to assess the circumstances under which a breach of Clause 2 could be ruled; this led to his further appeal letter.

In response to his appeal of the ruling of no breach of Clause 9.1, the companies had stressed their high regard for the Code based upon the fact that these materials were certified in accordance with Clause 14 and further stated that the materials were a competition and therefore each of the sketches should not be expected to stand alone as an advertisement.

However, the complainant noted that the original mailing invited GPs to write their own advertisement and stated 'You may even see your ad printed in a leading GP journal'. This indicated that there was

some intention to run winning entries as stand-alone advertisements. It seemed obvious therefore that all of the entries and the eventual winner of the competition should be able to stand alone as an advertisement and remain within the bounds of the evidence and the marketing authorization.

The complainant alleged that as the companies had not disputed that two of the thumbnail advertisements were in breach of Clause 7.2, the certification process for the mailing was below what should be expected and therefore a breach of Clause 9.1 should be ruled.

The complainant noted that the respondents drew attention to the differences between the entry criteria and composite outcome of CAPRIE, they also included other materials supporting the current licence for Plavix that was based upon the composite outcome of CAPRIE.

The complainant stated that the outcome of Cases AUTH/1588/5/04 and AUTH/1589/5/04 supported his assertion that the evidence did not support using clopidogrel before aspirin in the prevention of atherothrombotic events in stroke patients. This was because CAPRIE failed to show statistically better outcomes for clopidogrel over aspirin in patients with a recent history of stroke. This finding was investigated further when the subgroups were assessed for heterogenicity and it was suggested that the differences between the groups (MI, stroke and PAD) might not be down to chance.

The complainant stated that an advertisement for Plavix asking 'Is it time to change the management of stroke?' implied that prescribers should use Plavix before aspirin in these patients. None of the materials submitted along with the response supported this approach. In fact, aspirin was listed first in the materials produced by the Royal College of Physicians and there was no reason to question the place of aspirin based upon CAPRIE. The complainant found it more interesting that a trial to assess the efficacy of clopidogrel in relation to aspirin was used by the Royal College of Physicians to evidence the place of aspirin as first line anticoagulant treatment in stroke and patients with transient ischaemic attack.

The complainant noted the Panel's ruling in Cases AUTH/1588/5/04 and AUTH/1589/5/04 that promotion of Plavix for stroke alone was misleading. Despite this previous ruling, and the undertaking by the manufacturers to abide by this ruling, a Plavix advertisement that might be used as a stand-alone advertisement in a leading GP journal had been sent to GPs suggesting that stroke management needed a rethink. The complainant alleged that this indicated that despite the lack of superiority evidence for Plavix over aspirin and despite the previous rulings against a very similar advertisement the companies had allowed this mailing to be sent.

The complainant alleged that the standards followed in the certification of promotional materials must fall short of competent care if advertisements were certified when they were very similar to those that had already been ruled in breach of the Code and must also be recognised as a cumulative breach of the Code if the same clause was breached with an advertisement that was almost identical to one already ruled in breach. The complainant alleged for both of the reasons above, even in light of the fact that a new complaint had not been made, that a breach of Clause 2 could and should be ruled.

APPEAL BOARD RULING

The Appeal Board noted that two of the nine winning advertisements had been ruled in breach of Clause 7.2 of the Code. Doctors had been informed before they entered the competition that winning entries would comply with the Code. This had not been done. The Appeal Board considered that high standards had not been maintained in this regard and a breach of Clause 9.1 was ruled. The appeal on this point was successful. The Appeal Board did not consider that a ruling of a breach of Clause 2 was warranted as this was a sign of particular censure and reserved for such. The appeal on this point was unsuccessful.

Complaint received **14 October 2005**

Case completed **21 February 2006**

CASE AUTH/1776/10/05

PRIMARY CARE TRUST PHARMACEUTICAL ADVISER v MENARINI PHARMA

Promotion of Nebilet

A pharmaceutical adviser to a primary care trust (PCT) complained about a Nebilet (nebivolol) mailing sent by Menarini Pharma which consisted of a patient leaflet, a 'Dear Doctor' letter and a four page leaflet. The materials referred to the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).

The patient leaflet was headed 'Changing your atenolol prescription' and stated that a major trial had recently concluded and that some patients currently being treated with atenolol to control blood pressure could benefit from a change in prescription. The reader was then told that they could benefit by changing from atenolol to Nebilet. The leaflet listed a number of relevant patient organisations. It was stated that the leaflet was provided by Menarini as a service to the medical profession and patients.

The 'Dear Doctor' letter, headed 'In the light of ASCOT', explained that while the ASCOT study had shown the need to rethink the routine use of atenolol many patients might still require beta-blockade. The letter stated that it was feasible that 3rd generation beta-blockers, of which Nebilet was one, might offer advantages over atenolol. A more detailed description of the differences between Nebilet and atenolol was given in the four page leaflet which was entitled 'Where to go after ASCOT'.

The complainant alleged that Menarini was using ASCOT to advocate a switch from atenolol to nebivolol for the treatment of hypertension. ASCOT did not investigate the relative merits of one beta-blocker over another and did not support the claims that nebivolol was associated with an improved outcome over atenolol. The patient leaflet implied that the trial outcome suggested patients would benefit from a direct switch, a claim which the complainant considered could not be substantiated. The complainant considered that the materials were misleading and inappropriate.

The Panel noted that the patient leaflet had been the subject of a previous case, Case AUTH/1767/10/05 wherein it was alleged that the leaflet implied that Nebilet was involved in the ASCOT trial which was not so. In its ruling the Panel considered that those who read the patient leaflet would assume that the major trial (ie ASCOT) had shown that some patients currently being treated with atenolol would benefit by having their prescription changed to Nebilet, which was not so. The Panel considered that the leaflet was inaccurate and misleading and a breach of the Code was ruled. Further, as a result of its concerns about the impression given by the leaflet, the Panel had reported Menarini to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

Turning to the current case, Case AUTH/1776/10/05, the Panel considered that with regard to the patient leaflet, the matter at issue in Case AUTH/1767/10/05 encompassed that now before it. Menarini had accepted the ruling of a breach of the Code; the report for the Panel had yet to be heard by the Appeal Board. A breach of the Code was thus ruled.

In addition to the patient leaflet the complainant had also provided a copy of the 'Dear Doctor' letter. The first paragraph of the letter stated that ASCOT compared atenolol/ thiazide with amlodipine/perindopril in over 19,000 patients with hypertension. In that regard it was clear from the letter that ASCOT had not included Nebilet. However the letter went on to include comments from one of the lead investigators of the ASCOT study, and it was difficult to determine what was his personal opinion and what were findings from ASCOT. The lead investigator was quoted as stating 'it is feasible that the third generation ß-blockers may offer advantages over other drugs such as atenolol'. The product logo at the bottom right hand corner of each page of the letter incorporated the strapline 'More than just a simple ß-blocker'.

The Panel considered that the key message from the letter was that ASCOT had shown that hypertensive patients currently treated with atenolol would benefit from a change of therapy. It was not sufficiently clear that the recommendation that patients should be changed to Nebilet because it had advantages over atenolol was not part of the ASCOT study. In addition the Panel noted that there was no data directly comparing the outcomes with atenolol and those observed for Nebilet. The Panel considered that the letter was misleading and ruled a breach of the Code.

In considering this case the Panel noted that the four page leaflet had not been provided by the complainant but had been sent as part of the mailing and to the Authority by Menarini as part of its response. The Panel considered that it was an integral part of the mailing at issue and noted that it detailed the differences between Nebilet and atenolol, included the same product logo as noted above and the claim 'Nebivolol [Nebilet] may offer additional vascular protection in treating hypertension'. The Panel considered that its ruling of a breach of the Code also applied to the leaflet.

A pharmaceutical adviser to a primary care trust (PCT) complained about a Nebilet (nebivolol) mailing sent by A Menarini Pharma UK SRL. The mailing consisted of a patient leaflet (ref NEB/MJL/304/09.05), a 'Dear Doctor' letter (ref NEB/MJL/302/09.05) and a four page leaflet (ref NEB/MJL/303/09.05). The materials referred to the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).

The patient leaflet was headed 'Changing your atenolol prescription' and stated:

'A major trial involving a large number of patients in the UK and Scandinavia has recently been completed.

One of the conclusions of the trial is that some patients currently being treated with atenolol as part of their medication to control blood pressure could benefit from a change in prescription.

After considering your case, I believe you could benefit from a change in medication from atenolol to Nebilet. Whilst as effective at controlling blood pressure, Nebilet works in a different way to atenolol'.

The leaflet then listed a number of organisations which were sources of information about blood pressure and stated:

'Follow your doctor's advice carefully with regard to dosing and how to take Nebilet. It is possible that your doctor will invite you in for a check-up after changing your medication'.

It was also stated that the leaflet was provided by Menarini as a service to the medical profession and patients.

The 'Dear Doctor' letter, which outlined the issues and was headed 'In the light of ASCOT', explained that while ASCOT had shown the need to rethink the routine use of atenolol many patients might still require beta-blockade. The letter stated that it was feasible that 3rd generation beta-blockers, of which Nebilet was one, might offer advantages over atenolol. A more detailed description of the differences between Nebilet and atenolol was given in the four page leaflet which was entitled 'Where to go after ASCOT'.

COMPLAINT

The complainant alleged that Menarini was using ASCOT to advocate a switch from atenolol to nebivolol for the treatment of hypertension. ASCOT did not investigate the relative merits of one beta-blocker over another and did not support the claims that nebivolol was associated with an improved outcome over atenolol. The implication of the patient leaflet was that the trial outcome suggested patients would benefit from a direct switch, a claim the complainant considered could not be substantiated. The complainant considered that the materials were misleading and inappropriate.

When writing to Menarini, the Authority asked it to respond in relation to Clauses 7.2 and 20.2 of the Code.

RESPONSE

Menarini explained that the mailing was sent because it was important to remind doctors that 'not all beta-blockers are atenolol'. This was to try to redress the balance in the face of a flurry of press articles making sweeping statements and assuming that specific results from an atenolol-based treatment in ASCOT applied to all beta-blockers.

ASCOT showed that in hypertension, outcomes were less favourable with an atenolol-based regimen than with an amlodipine/perindopril regimen. These results meant that GPs across the UK were reviewing the treatment of large numbers of patients currently treated with atenolol, a widely used first generation beta-blocker. As a result, there was likely to be a significant reduction in atenolol use and an increase in amlodipine/perindopril. This was entirely appropriate. However, successful treatment of hypertension frequently required the use of several adjunctive medicines. The amlodipine/perindopril regime was unlikely to be sufficient to ensure that every patient reached their blood pressure target and, in addition, large numbers would not tolerate the treatment (in ASCOT 25% patients stopped treatment due to adverse events). Therefore, for reasons of effectiveness or tolerability, a variety of alternative and adjunctive treatments (angiotensin II receptor antagonists, third generation beta-blockers, etc) would be used to treat some patients. As Nebilet was an established third generation beta-blocker with characteristics very different from atenolol, and was significantly less expensive than angiotensin II receptor antagonists, it was an appropriate alternative for some hypertensive patients.

Menarini did not consider that the patient leaflet implied that the ASCOT outcomes suggested that patients would benefit from a switch from atenolol to Nebilet. The leaflet clearly stated that ASCOT concluded that many patients might need a change from atenolol. It also stated that the doctor considered Nebilet to be the appropriate alternative treatment for the individual patient to whom the leaflet was given and, that while Nebilet was as effective as atenolol in controlling blood pressure, it worked in a different way. The leaflet did not mention outcomes for either medicine.

Menarini thus did not consider that the leaflet was misleading, or that it implied anything other than it stated. It was factually correct.

Menarini denied breaches of Clauses 7.2 and 20.2. The leaflet was to be given by a doctor to a patient, as part of the explanation for their change in medicine. The leaflet had not been provided unsolicited by a pharmaceutical company to a patient but provided as an 'aid to change' service for doctors to use at their discretion. No influence other than usual accepted marketing practices had been employed to facilitate a change; the choice was entirely with the doctor.

Menarini explained that the patient leaflet was an example of the type of material used routinely to augment verbal explanations given to patients by doctors. As a pharmaceutical adviser, the complainant might not be fully familiar with the use of this type of support material by GPs, and this might in part explain the misinterpretation.

Menarini noted that the complainant did not specifically refer to the 'Dear Doctor' letter, but was clearly concerned that the material implied that ASCOT compared atenolol and Nebilet. A Menarini disagreed; there was nothing in the letter to imply that Nebilet was included in ASCOT. The first sentence of the letter was particularly clear on this point: 'The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) compared the frequently used antihypertensive treatments atenolol/thiazide diuretic with amlodipine/perindopril in over 19,000 patients with hypertension'.

Menarini noted the allegation that a claim has been made of improved outcomes with Nebilet compared

with atenolol; and that ASCOT had been used to support such a claim. The company disagreed; there was nothing in the letter to suggest a claim of improved outcomes compared with atenolol. Menarini was unaware of any evidence directly comparing the outcomes of these two medicines.

Menarini noted that the complainant had not referred to the four page leaflet 'Where to go after ASCOT'. This leaflet directly compared Nebilet with atenolol but although it referred to the distinct differences between Nebilet and atenolol, no reference to comparative outcomes was made.

PANEL RULING

The Panel noted that the patient leaflet had been the subject of a previous case, Case AUTH/1767/10/05 wherein it was alleged that the leaflet implied that Nebilet was involved in the ASCOT trial which was not so. In its ruling the Panel considered that those who read the patient leaflet would assume that the major trial (ie ASCOT) had shown that some patients currently being treated with atenolol would benefit by having their prescription changed to Nebilet, which was not so. The Panel considered that the leaflet was inaccurate and misleading and a breach of Clause 20.2 was ruled. Further, as a result of its concerns about the impression given by the leaflet, the Panel had reported Menarini to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

Turning to the current case, Case AUTH/1776/10/05, the Panel considered that with regard to the patient leaflet, the matter at issue in Case AUTH/1767/10/05 encompassed that now before it. Menarini had accepted the ruling of a breach of Clause 20.2; the report for the Panel had yet to be heard by the Appeal Board. A breach of Clause 20.2 was thus ruled.

In addition to the patient leaflet the complainant had also provided a copy of the 'Dear Doctor' letter. The first paragraph of the letter stated that ASCOT compared atenolol/thiazide with amlodipine/perindopril in over 19,000 patients with hypertension. In that regard it was clear from the letter that ASCOT had not included Nebilet. However the letter went on to include comments from one of the lead investigators of the ASCOT study, and it was difficult to determine what was his personal opinion and what were findings from ASCOT. The lead investigator was quoted as stating 'it is feasible that the third generation b-blockers may offer advantages over other drugs such as atenolol'. The product logo at the bottom right hand corner of each page of the letter incorporated the strapline 'More than just a simple ß-blocker'.

The Panel considered that the key message from the letter was that ASCOT had shown that hypertensive patients currently treated with atenolol would benefit from a change of therapy. It was not sufficiently clear that the recommendation that patients should be changed to Nebilet because it had advantages over atenolol was not part of the ASCOT study. In addition the Panel noted that there was no data directly comparing the outcomes with atenolol and those observed for Nebilet. The Panel considered that the letter was misleading and ruled a breach of Clause 7.2.

In considering this case the Panel noted that the four page leaflet had not been provided by the complainant but had been sent as part of the mailing and to the Authority by Menarini as part of its response. The Panel considered that it was an integral part of the mailing at issue and noted that it detailed the differences between Nebilet and atenolol, included the same product logo as noted above and the claim 'Nebivolol [Nebilet] may offer additional vascular protection in treating hypertension'. The Panel considered that its ruling of a breach of Clause 7.2 would also apply to the leaflet and requested that Menarini be so advised.

Complaint received **21 October 2005**

Case completed **12 December 2005**

CASES AUTH/1779/11/05 and AUTH/1780/11/05

PROCTER & GAMBLE and SANOFI-AVENTIS v ROCHE and GLAXOSMITHKLINE

Bonviva leavepiece

Procter & Gamble and Sanofi-Aventis submitted a joint complaint about a leavepiece for Bonviva (ibandronic acid) issued by Roche and GlaxoSmithKline. The leavepiece entitled 'Faced with 52 or 12 tablets a year, what would patients prefer?' compared Bonviva one tablet a month, with alendronate (Fosamax), one tablet a week, for the treatment of osteoporosis. Bonviva was indicated for the treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures had not been established. Fosamax once-weekly was also indicated for the treatment of postmenopausal osteoporosis (PMO) to prevent fractures. It reduced the risk of vertebral and hip fracture. The leavepiece was for primary care representatives to use with pharmacists.

Procter & Gamble and Sanofi-Aventis stated that in 2001 the European regulatory guidelines on the evaluation and licensing of medicines for PMO clearly differentiated in the effectiveness of fracture risk reduction (vertebral and/or hip) of an osteoporosis treatment in a postmenopausal population, notwithstanding and even stressing the significance of a potential omission of fracture risk reduction effect if efficacy was not demonstrated at the spine and hip.

The complainants alleged that the claim in the leavepiece that Bonviva was for 'postmenopausal osteoporosis' was all encompassing; it implied proven efficacy in risk reduction of all osteoporotic fractures (vertebral and hip) as assessed by the regulatory authorities. This was not so; Bonviva once a month was indicated for the 'Treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established'. Thus Bonviva had demonstrated efficacy in reducing vertebral fractures, but had not demonstrated such an effect at the hip and hence its promotion should explicitly state where it had proven and licensed efficacy and not remain ambiguous and open to misinterpretation. This was reinforced by looking at the indications for other osteoporosis therapies, such as alendronate and risedronate, both of which were licensed specifically to reduce the risk of both vertebral and hip fractures. A hip fracture was the most debilitating fracture in osteoporosis with one in five women dying within one year. It was therefore important to patient safety that physicians were fully aware of the benefits and limitations of therapy when reading promotion which might influence their prescribing.

Procter & Gamble and Sanofi-Aventis alleged that the claim 'Bonviva once-monthly for postmenopausal osteoporosis' went beyond the licensed indication as well as the evidence base.

The Panel noted that Bonviva was indicated for the 'Treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established'. In the leavepiece, however, the second sentence of the indication had been omitted from the prescribing information.

The purpose of the leavepiece was, *inter alia*, to compare the patient acceptability of taking Bonviva once a month with that of taking alendronate once a week. The claim 'Bonviva once-monthly for postmenopausal osteoporosis' appeared as the heading to a page which featured a pie chart depicting patient preference for the two therapies. The Panel considered that many readers would assume that it was a simple choice between once-weekly and once-monthly therapy and that in all other respects the two medicines were equal. Prescribers might be persuaded to change patients from alendronate to Bonviva in the belief that the proven benefits of therapy were the same for each medicine. This was not so. Alendronate could be used to reduce the risk of vertebral and hip fracture whereas the efficacy of Bonviva on hip fractures had not been established.

The Panel noted that there were three third generation bisphosphonates licensed for the treatment of PMO (Actonel, Fosamax and Bonviva) all of which could be used to decrease the risk of vertebral fracture. The Panel thus considered that a decrease in the risk of vertebral fracture would be seen by prescribers to be an accepted benefit of therapy with these agents. The medicines differed, however, in their licensed effects on hip fracture; Fosamax decreased the risk of hip fracture; Actonel decreased the risk of hip fracture but only in established PMO and the efficacy of Bonviva on hip fractures had not been established. Given the differences between the products, and the clinical consequences of hip fracture, the Panel considered that it was beholden upon companies to be abundantly clear about the terms of their product's marketing authorization.

The claim 'Bonviva once-monthly for postmenopausal osteoporosis' headed a page which compared Bonviva with alendronate. The Panel noted its comments above and considered that by association readers would assume that Bonviva decreased the risk of both vertebral and hip fractures which was not so. The Panel considered that the failure to note that efficacy on hip fractures had not been established meant that the claim at issue, within the context of which it appeared, was misleading and incapable of substantiation. Breaches of the Code were ruled. The Panel considered that the claim, in the context in which it appeared, implied that Bonviva reduced the risk of hip fracture which was inconsistent with the particulars listed in the marketing authorization. The Panel ruled a breach of the Code.

Upon appeal by Roche and GlaxoSmithKline. the Appeal Board noted that Bonviva was indicated for the 'Treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established'.

The Appeal Board also noted that the 2001 European regulatory guidelines on PMO stated 'From the regulatory viewpoint two therapeutic indications are recognised, ie.: prevention of osteoporosis in postmenopausal women … treatment of osteoporosis. The applicant will be requested to study the effect of the investigated drug on both spinal and femoral (not all non-vertebral) fractures …. The indication will be granted only if anti-fracture efficacy has been demonstrated at, at least, one site and no deleterious effect has been shown at the other site. In the "indication" part of the SPC, it will be clearly specified if anti-fracture efficacy has been shown at the spine and/or at the hip. Failure to demonstrate anti-fracture efficacy at the second site will also appear in this section of the SPC'. The Appeal Board considered that the statement, 'Efficacy on femoral neck fractures has not been established' in the indication section of the Bonviva SPC provided the evidence base for the indication, which was the treatment of PMO.

The Appeal Board noted that the leavepiece referred to Chesnut *et al* (2004) and included a positive claim for the reduction in risk of vertebral fracture. Chesnut *et al* had not been powered to assess hip fracture efficacy. There was no mention of hip fractures in the leavepiece. The Appeal Board considered that the claim 'Bonviva once monthly for postmenopausal osteoporosis', in the context of a comparison of patient preference for Bonviva or alendronate, did not imply that efficacy data was available to show that Bonviva decreased the risk of hip fractures. The comparison was between two bisphosphonates which were both indicated for the treatment of PMO.

The Appeal Board did not consider that the claim, in the context of the page, was sufficient to mislead in relation to the evidence base of the medicine and so it was not inconsistent with the Bonviva SPC. The Appeal Board ruled no breach of the Code. The Appeal Board considered that the claim was not misleading and could be substantiated and thus ruled no breaches of the Code.

Procter & Gamble and Sanofi-Aventis alleged that the claim 'Faced with 52 or 12 tablets a year, what would patients prefer?' and use of the BALTO (Bonviva Alendronate Trial in Osteoporosis) study to claim patient preference for a monthly bisphosphonate compared with a weekly bisphosphonate were misleading on two accounts. Firstly they reinforced the misinterpretation implied by the claim 'Bonviva once-monthly for postmenopausal osteoporosis', since the reader would assume that the efficacy of both therapies was the same. Secondly, such a study was open to misinterpretation and the results misleading if the patients involved made their choice of preferred therapy assuming that Bonviva and alendronate had the same efficacy. Patients were not explicitly informed about the differences in the licensed indications/efficacy between the two therapies. It was therefore irresponsible to make a strong promotional claim that patients preferred a monthly therapy based upon a study that did not account for important influencers of patients' preference. The companies alleged that use of this study to claim a patient preference for Bonviva once-monthly over alendronate once-weekly was misleading.

The Panel did not consider that the claim 'Patients prefer a monthly to a weekly bisphosphonate' was self evident as submitted by the respondents. Some patients might find it easier to establish a routine of taking a tablet on the same day every week than on the same date every month. The Panel noted that the method of administration of oral bisphosphonates would impact on patients. Fosamax (alendronate) (once weekly) had to be taken at least 30 minutes before the first food, beverage or medicine of the day with plain water only. Patients should not lie down until after their first food of the day which should be at least 30 minutes after taking the tablet. The dosing instructions for Bonviva 150mg were different in that the medicine had to be taken after an overnight fast of at least 6 hours and one hour before the first food, drink (other than water) or medicine of the day. Patients should not lie down for one hour after taking Bonviva.

The Panel noted that the patients in the study had not been informed of the differences in the indications for Bonviva and alendronate. This might have influenced their decision as to which medicine to take. It appeared from the data presented in the leavepiece that the only difference was in the dosing interval and not in the method of administration or indications. In addition given the context of the page readers would assume that alendronate and Bonviva had the same indication and this was not so. The Panel considered that the comparison was unfair and breaches of the Code were ruled.

Upon appeal by Roche and GlaxoSmithKline the Appeal Board noted that the BALTO study was started before the marketing authorization for Bonviva had been granted and thus before the evidence base for the product was fully assessed. Patients could not have known that, in contrast to alendronate, efficacy on hip fractures would not be established for Bonviva. In that regard the patients did not have the full facts about Bonviva and thus, in the Appeal Board's view, would not have been able to express a genuine, well informed preference between it and alendronate. In that regard the Appeal Board considered that the comparison was unfair and was not based on an up-to-date evaluation of all the evidence. The Appeal Board upheld the Panel's ruling of breaches of the Code.

Procter & Gamble Pharmaceuticals UK Limited and Sanofi-Aventis submitted a joint complaint about the promotion of Bonviva (ibandronic acid) by Roche Products Limited and GlaxoSmithKline UK Limited. At issue was a gate folded, 6 page leavepiece (ref BNV/DAP/05/20703/1 20783529 P117201) entitled 'Faced with 52 or 12 tablets a year, what would patients prefer?' which, *inter alia*, compared Bonviva one tablet a month, with alendronate (Fosamax), one tablet a week, for the treatment of osteoporosis. Bonviva was indicated for the treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures had not been established. Fosamax once-

weekly was also indicated for the treatment of postmenopausal osteoporosis (PMO) to prevent fractures. It reduced the risk of vertebral and hip fracture. The leavepiece was for primary care representatives to detail and leave with pharmacists.

1 Claim 'Bonviva once-monthly for postmenopausal osteoporosis'

COMPLAINT

The International Osteoporosis Foundation defined osteoporosis as a disease in which the density and quality of bone were reduced, leading to weakness of the skeleton and increased risk of fracture, particularly of the spine, wrist, hip, pelvis and upper arm. In other words osteoporosis affected both the axial (ie vertebral) and appendicular (ie non-vertebral eg hip) sites of the skeleton.

Procter & Gamble and Sanofi-Aventis stated that in 2001 the European Agency for the Evaluation of Medicinal Products (EMEA) issued, via the Committee for Proprietary Medicinal Products (CPMP), a guideline on the evaluation and licensing of medicines for PMO in its Note for Guidance on Postmenopausal Osteoporosis in Women. The CPMP guideline clearly differentiated in the effectiveness of fracture risk reduction (vertebral and/or hip) of an osteoporosis treatment in a postmenopausal population, notwithstanding and even stressing the significance of a potential omission of fracture risk reduction effect if efficacy was not demonstrated at the spine and hip.

The claim that Bonviva was for 'postmenopausal osteoporosis' was therefore all encompassing and implied that it had proven efficacy in risk reduction of all osteoporotic fractures (both vertebral and hip sites) and had been assessed by the regulatory authorities as efficacious at all sites. However, this was clearly not the case, as explicitly set out in the Bonviva 150mg once a month indication, which stated: 'Treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established.'

Thus evidently Bonviva had demonstrated efficacy in reducing vertebral fractures, but had not demonstrated such an effect at the hip and hence its promotion should explicitly state where it had proven and licensed efficacy and not remain ambiguous and open to misinterpretation.

This was reinforced by looking at the indications for other osteoporosis therapies, such as alendronate and risedronate, both of which were licensed specifically to reduce the risk of both vertebral and hip fractures.

A fracture of the hip was the most debilitating fracture in osteoporosis with one in five women dying within one year of fracture. It was therefore important to patient safety that a physician was fully aware of the benefits and limitations of the therapy when reading promotion which might influence the prescribing decision.

Roche had stated that the prescribing information at the back of the leavepiece made it clear what the indication for Bonviva was. In the complainants' view this was insufficient and at conflict with the Code and established practice, each page of promotional copy should be capable of standing alone, with the claims clearly qualified on the page they were used.

The claim 'Bonviva once-monthly for postmenopausal osteoporosis' therefore went beyond the licensed indication as well as the evidence base. Breaches of Clauses 3.2, 7.2 and 7.4 of the Code were alleged.

RESPONSE

Roche and GlaxoSmithKline refuted the allegations and submitted that the claim was clear as to the disease area for which Bonviva was suitable and made no claims regarding fracture efficacy at any site. In contrast to the allegation the companies noted that Bonviva was indicated in all patients with PMO (assuming there were no contra-indications). The companies noted that the wording of the indication section of the Bonviva licence was determined by the EMEA guideline on the licensing of products for PMO published in 2001. In Section 2 of this guideline, the CPMP clearly stated that in PMO, 'From the regulatory viewpoint, two therapeutic indications are recognised', namely the indication for prevention and the indication for treatment. This was further supported by EMEA published documents, including the announcement on the positive opinion granted for Bonviva 'to treat osteoporosis' as well as wording in the ibandronic acid patient information leaflet (PIL).

Section 2 of the EMEA guideline also clarified that any additional wording in '…the indication part of the SPC' [summary of product characteristics] was only intended to elucidate the nature of the data on which the indication was granted as additional information and did not define different types or classes of indications for specific fracture locations. As such it was clear that regulatory authorities simply required a reduction in fracture risk to be demonstrated in at least one site, and with no detriment at other sites, for approval of a PMO indication.

Thus it was clear that the statement regarding the information relating to fracture efficacy contained within the indication section of the SPC reflected the EMEA guidance and did not limit the target population suitable for Bonviva.

It did, of course, affect promotional claims that might be made about specific fracture risk reduction. In the material in question, claims of fracture risk reduction were clearly and explicitly labelled as being vertebral. No claims were made for reduction of risk of hip fracture. Even the casual reader would have been clear on the type of fractures claims were made for.

The companies submitted that the claim 'Bonviva once-monthly for postmenopausal osteoporosis' was in accordance with the terms of the marketing authorization and consistent with the particulars in the SPC. The discussion of reduction in vertebral fracture risk was clear, unambiguous and substantiated. There were no claims in the leavepiece for efficacy at other fracture sites. As such the item did not breach Clauses 3.2, 7.2 or 7.4 of the Code.

PANEL RULING

The Panel noted that the Bonviva 150mg SPC stated it was indicated for the 'Treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established'. In the leavepiece, however, the second sentence of the indication had been omitted from the prescribing information.

The Panel noted that the purpose of the leavepiece was, *inter alia*, to compare the patient acceptability of taking Bonviva once a month with that of taking alendronate once a week. The claim 'Bonviva once-monthly for postmenopausal osteoporosis' appeared as the heading to a page which featured a pie chart depicting patient preference for the two therapies. The Panel considered that many readers would assume that it was a simple choice between once-weekly and once-monthly therapy and that in all other respects the two medicines were equal. Prescribers might be persuaded to change patients from alendronate to Bonviva in the belief that the proven benefits of therapy were the same for each medicine. This was not so. Alendronate could be used to reduce the risk of vertebral and hip fracture whereas the efficacy of Bonviva on hip fractures had not been established.

The Panel noted that there were three third generation bisphosphonates licensed for the treatment of PMO (Actonel, Fosamax and Bonviva) all of which could be used to decrease the risk of vertebral fracture. The Panel thus considered that a decrease in the risk of vertebral fracture would be seen by prescribers to be an accepted benefit of therapy with these agents. The medicines differed, however, in their licensed effects on hip fracture; Fosamax decreased the risk of hip fracture; Actonel decreased the risk of hip fracture but only in established PMO and the efficacy of Bonviva on hip fractures had not been established. Given the differences between the products, and the clinical consequences of hip fracture, the Panel considered that it was beholden upon companies to be abundantly clear about the terms of their product's marketing authorization.

The claim 'Bonviva once-monthly for postmenopausal osteoporosis' headed a page which compared Bonviva with alendronate. The Panel noted its comments above and considered that by association readers would assume that Bonviva decreased the risk of both vertebral and hip fractures which was not so. The Panel considered that the failure to note that efficacy on hip fractures had not been established meant that the claim at issue, within the context of which it appeared, was misleading and incapable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled. The Panel considered that the claim, in the context in which it appeared, implied that Bonviva reduced the risk of hip fracture which was inconsistent with the particulars listed in the marketing authorization. The Panel ruled a breach of Clause 3.2 of the Code.

During its consideration of this case the Panel was concerned about the omission of the statement 'Efficacy on femoral neck fractures had not been established' from the prescribing information. It considered that incomplete information had been given about the authorized indication and thus the prescribing information was misleading. The Panel requested that Roche and GlaxoSmithKline be advised of its views.

APPEAL BY ROCHE AND GLAXOSMITHKLINE

Roche and GlaxoSmithKline were disappointed that the Panel had ruled breaches with regards to the interpretation of their European marketing authorization which had been based upon proof of efficacy at multiple sites and enabled them to promote 'Bonviva once-monthly for postmenopausal osteoporosis'. The companies agreed that the wording in the indications section of the SPC 'Treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established' might appear to be restrictive. However, this wording was a result of the EMEA guidance issued in 2001 and the intention was not to restrict the licence to vertebral fractures. The additional words regarding vertebral fractures and hip fractures highlighted the evidence base, but did not restrict the target population as this would be impossible in practice.

The companies submitted that this was further supported by EMEA published documents, including the announcement on the positive opinion granted for Bonviva 'to treat osteoporosis', and the EMEA-approved PIL for Bonviva which stated that the product was prescribed 'to treat osteoporosis'. Under the legal framework of the centralised procedure, the labelling and leaflet formed part of the community decision. Article 59 of 2001/83/EC stated that the package leaflet should be drawn up in accordance with the SPC.

The companies submitted that since the package leaflet was reviewed by the CPMP and indeed was annexed within the committee's opinion this confirmed that the licensed indication was for use in PMO without qualification. As such, the claim 'Bonviva once-monthly for postmenopausal osteoporosis' was in accordance with the terms of its marketing authorization and was not inconsistent with the particulars listed in its SPC. Furthermore the PIL stated 'Bonviva prevents loss of bone from osteoporosis, and helps to rebuild bone. Therefore Bonviva makes bone less likely to break'. Nowhere in the PIL was it stated that efficacy was limited with regard to the risk for any particular type of fracture. The recent entry for Bonviva in the British National Formulary (BNF) stated the indication as 'Treatment of postmenopausal osteoporosis', in contrast to the entry underneath it for Fosavance where there was a restriction on the licence.

The companies submitted that by its very nature, PMO was a systemic condition, affecting vertebral and non-vertebral sites. Treatments were licensed on the basis of their systemic activity at all skeletal sites, as had been demonstrated for Bonviva. All data showed Bonviva was an effective bisphosphonate at all sites. The beneficial effect on bone mineral density (BMD) and other markers of bone turnover was seen

in all parts of the affected skeleton (including both the spine and hip) as described in section 5 of the SPC. This was the case in many other disease areas where well validated surrogate markers were used for regulatory approval.

In PMO, vertebral fractures were nearly twice as common as hip fractures (120,000 versus 70,000) and therefore fewer patients were needed to adequately power a trial to show reduction in vertebral fractures than to show reduction in hip fractures. Chesnut *et al* (2004) demonstrated an absolute reduction in hip fractures with Bonviva in a subgroup of high risk patients as the higher event rate in this group meant that they were more likely to get fractures and therefore demonstrate a statistically significant difference.

The companies submitted that prescribers could not identify which bone a PMO patient was going to break next and therefore it did not make clinical sense to interpret the licence wording as if there was a subgroup of patients who were only at risk of vertebral fracture and not other types of fracture. In the material at issue, all claims of fracture risk reduction were clearly and explicitly labelled as being vertebral. No claims were made for reduction of hip fracture. The fracture sites referred to within the claims were clear even to the casual reader.

The companies noted that the Panel considered that many readers would assume it was a simple choice between once-weekly and once-monthly therapy and that in all other respects the two medicines were equal. The companies submitted that in terms of the type of patient to be treated and the likely risk/benefit profile then this was in fact the case. When choosing between two bisphosphonates, the prescriber was faced with the choice between a well established product that had been proven to reduce fractures at both hip and spine (eg alendronate) and a new one that had been proven to reduce fracture in the spine but not the hip (Bonviva) but had (like alendronate) proven efficacy in increasing BMD at multiple sites.

No head to head studies had been carried out to compare the clinical efficacy of Bonviva with that of alendronate, and so it was impossible to decide that one was definitively more efficacious than the other as comparisons across studies was fraught with difficulty. Daily alendronate had been proven to reduce both vertebral and non-vertebral fractures as would be expected from a product at this stage in its life-cycle. The absence of proof of a statistically significant reduction in the risk for hip fractures did not mean that Bonviva was not effective in relation to hip fractures; it meant it had not yet been proven.

The companies reiterated that the evidence provided in the marketing application for Bonviva fulfilled the requirements of the EMEA to permit it to grant an unrestricted licence PMO. The companies thus disagreed with the Panel's interpretation of the Bonviva licence and appealed the ruling of a breach of Clause 3.2.

The companies noted that the Panel had also ruled the claim 'Bonviva once-monthly for postmenopausal osteoporosis' in breach of Clauses 7.2 and 7.4. The companies submitted that because the claim was in accordance with the marketing authorization, it was accurate, fair and not misleading. All claims of fracture risk reduction clearly and explicitly referred to vertebral fractures alone. No claims were made for reduction of hip fracture. The companies appealed the rulings of breaches of Clauses 7.2 and 7.4.

COMMENTS FROM PROCTER & GAMBLE AND SANOFI-AVENTIS

Procter & Gamble and Sanofi-Aventis noted that Roche and GlaxoSmithKline had submitted that their marketing authorization had been based upon proof of efficacy at multiple sites which enabled them to promote Bonviva once-monthly for PMO. The companies noted that the EMEA had given a restricted licence, specifically stating that only vertebral fracture efficacy was achieved and that there was an absence of hip fracture efficacy. Bonviva once-monthly only had data to support vertebral fracture efficacy and not at other sites. This was reflected in the indication. Data supporting its efficacy at other sites was disparate with a positive effect being demonstrated in a very small subgroup of patients (13%) and a negative effect demonstrated in the remaining population (87%). It was therefore inappropriate to claim fracture efficacy at multiple sites or indeed any site other than the vertebrae based on this data.

The companies further noted that Roche and GlaxoSmithKline had stated that treatments for osteoporosis were licensed on the basis of their systemic activity at all skeletal sites, as had been demonstrated for Bonviva, and that all data showed Bonviva was an effective bisphosphonate at all sites. The companies alleged that treatments for osteoporosis were clearly licensed on demonstrated fracture efficacy at the vertebrae and/or hip, regardless of demonstrated systemic activity via BMD or bone turnover markers. Bonviva had only demonstrated vertebral fracture incidence reduction and had no data that demonstrated fracture efficacy at any other site or all sites, hence the restrictions in its licence.

Procter & Gamble and Sanofi-Aventis noted the claim 'Bonviva once-monthly for postmenopausal osteoporosis' and stated that the key question which must be addressed was whether Bonviva once-monthly was licensed in the UK to claim efficacy in the risk reduction of hip fractures. Currently in the promotional material of Bonviva once-monthly, Roche and GlaxoSmithKline made broad statements regarding the all encompassing efficacy (both vertebral and hip fracture reduction) of Bonviva. However, it was clear from the SPC that the product did not have efficacy at the hip.

The companies alleged that it was clear from the appeal that Roche and GlaxoSmithKline continued to interpret and extrapolate the wording of the EMEA guidance and approval documentation inappropriately. To support their view, the companies referred to the regulatory requirements for osteoporosis therapies within Europe, which were clearly explained and without ambiguity.

The CPMP Note for Guidance on postmenopausal osteoporosis in women, CPMP/EWP/552/95/rev 1 stated:

Section 2 Mode of Treatment

'Treatment of osteoporosis aims to decrease incident fractures.'

Section 4.3.1 Fractures

'In the indication treatment of osteoporosis, fracture information must be available.'

'The primary variable should be based on the occurrence of new axial and peripheral fractures.'

'Vertebral and hip fractures are to be studied separately in confirmatory trials'

Section 4.3.2 Bone Mineral Density (BMD)

'BMD is not considered an appropriate surrogate for fracture reduction in therapeutic confirmatory treatment study.'

Section 4.3.4 Biochemical markers

'BMD and an appropriate biochemical marker of bone turnover (eg….) should be considered as primary variable in Phase II dose finding trials. However, they are not considered an appropriate surrogate in therapeutic confirmatory treatment studies.'

5.3.2 Treatment of osteoporosis

'…therapeutic trials in osteoporosis should be designed with the incidence of patients with new fractures as the primary efficacy variable.'

'…., BMD cannot serve as satisfactory surrogate end-point for the documentation of clinically relevant efficacy.'

The companies stated that there was, therefore, no ambiguity in this guidance document. The requirements for the indication 'Treatment of postmenopausal osteoporosis' were fracture studies demonstrating a reduction in the incidence of osteoporotic fractures. Regardless of the opinions of Roche and GlaxoSmithKline that the BMD efficacy of Bonviva once-monthly at multiple sites should be extrapolated to prove fracture efficacy at multiple sites, it was clearly the opinion and intent of the CPMP that efficacy must be proven by a significant reduction in fractures at each site. In addition the CPMP Note for Guidance stated:

Section 2 Mode of Treatment

'From the regulatory viewpoint, two therapeutic indications are recognized, i.e.:

Prevention of osteoporosis….

- *Treatment of osteoporosis. The applicant will be requested to study the effect of the investigated drug on both spinal and femoral (not all non-vertebral) fractures. This should be done in properly designed and adequately powered studies. The indication will be granted only if anti-fracture efficacy has been demonstrated at, at least, one site and no deleterious effects have been shown at the other site. In the 'indication' part of the SPC, it will be clearly specified if anti-fracture efficacy has been shown at the spine and / or at the hip. Failure to demonstrate anti-fracture efficacy at the second site will also appear in this section of the SPC.'*

The companies alleged that once again the CPMP was unambiguous in defining how the indication section of the SPC would be written based on the evidence from the supporting clinical trials. The guideline required efficacy to be shown separately at the hip and vertebral sites since the type of bone was predominantly different (ie cortical and trabecular respectively) and hence efficacy at the hip could not be assumed just because it had been shown at the spine.

The companies alleged that the data for Bonviva once-monthly showed that it reduced the risk of vertebral fractures, but did not have a positive effect on the risk of hip fracture. Thus, on the basis of the published guidelines, CHMP (Committee for Human Medicinal Products, the new name for CPMP) had granted Bonviva once-monthly the following indication in its SPC: 'Treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established.'

The companies noted, for Fosamax once weekly which had demonstrated vertebral and hip fracture efficacy, the licensed indication appeared as: 'Treatment of postmenopausal osteoporosis. 'Fosamax' reduces the risk of vertebral and hip fractures.'

The companies noted for Actonel once a week vertebral and hip fracture efficacy had also been demonstrated, but the patients populations differed slightly: 'Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures.'

The companies submitted that the point of accurately defining the efficacy results, site of action and patient populations in the indication section of the SPC, was to restrict the use of the medicine, by ensuring the product was used within the confines supported by its clinical studies, to guide prescribing and to protect patient safety. If the intention was to only highlight the evidence base, then all of the above therapies would have the indication 'Treatment of postmenopausal osteoporosis', with discussions of the evidence base occurring in Section 5.1 of the SPC only, which was clearly not the case.

The companies submitted that the intent of CHMP was further confirmed in the draft CHMP guidance (Dec 2005) on the 'evaluation of new medicinal products in the treatment of primary osteoporosis'. This document would replace the current CPMP guidance (CPMP/EWP/552/95/rev 1) and reinforced how the CHMP osteoporosis guidance left no room for any ambiguity ie:

Section 2 Aim of Treatment

'From the regulatory viewpoint, the therapeutic indication will generally be the treatment of osteoporosis in postmenopausal women at high risk of a fracture, …. The indication may be restricted, e.g. to the effect on the axial skeleton, depending on the results of the clinical trials.'

Procter & Gamble and Sanofi-Aventis noted that Roche and GlaxoSmithKline had claimed that if the EMEA had intended to restrict the indication, then this would be impossible to implement in practice;

this was untrue. From the epidemiology of osteoporosis it was clear that younger patients were more prone to vertebral fractures than hip fractures, thus therapies which had only demonstrated vertebral fracture efficacy, like Bonviva once-monthly, could potentially be used in this population.

The companies submitted that Roche and GlaxoSmithKline had supported their appeal by referring to the EMEA announcement on the positive opinion granted for Bonviva 'to treat osteoporosis', but failed to state that the complete indication shown above was explicitly called out in this document, as well as the European Public Assessment Report.

The companies further noted that in their appeal Roche and GlaxoSmithKline had cited the EMEA approved PIL for Bonviva once-monthly, as support for their broad claim 'to treat osteoporosis'. This was puzzling, since the PIL was subservient to the SPC and did not, under any conditions, supplant the information in the SPC. Information on how a medicine should be used was provided to doctors and pharmacists in the SPC and not in the PIL. These two key points were reflected in the wording of Clause 3.2 of the Code which stated: 'The promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics', rather than citing the PIL.

In addition, the companies alleged that the erroneous omission of key information from the Bonviva once monthly PIL (ie that Bonviva was only licensed for the treatment of PMO: to prevent vertebral fractures), should not be used to justify further misleading communications, but should be rapidly rectified by updating the PIL. The consequences of perpetuating such misleading information in PILs could be seen in the design and results of Roche and GlaxoSmithKline's own BALTO study, as discussed later.

The companies noted that Roche and GlaxoSmithKline had referred to the recent entry in the BNF as support for their broad claim 'Treatment of postmenopausal osteoporosis'. However, the companies submitted that Roche and GlaxoSmithKline appeared to be ignoring the fact that the SPC was the presiding document for promotional claims, and that all other documents supported or clarified the information contained therein. Until an appropriate regulatory agency had evaluated new clinical data, not even gold standard clinical studies in the most prestigious publications enabled a pharmaceutical company to broaden its licensed indication in promotional materials.

The companies noted that Roche and GlaxoSmithKline further claimed that an absolute reduction in hip fractures with Bonviva had been demonstrated in a subgroup of high risk patients; on the data available this was untrue. The data presented in Chesnut *et al* and the FDA Medical Review were a post hoc analysis of a subgroup of patients assessing a composite of non-vertebral fractures, not just hip fractures. The data needed careful interpretation, as only the sub population with a baseline femoral neck BMD T-score <–3SD demonstrated a benefit and this represented a mere 13% of the trial population (ITT). The remaining 87%, showed an increase in non-vertebral fracture incidence in the Bonviva treated population, and did not show a benefit versus the control group. In fact more non-vertebral fractures were observed in the Bonviva treated patients than in the control group. In addition using the official WHO definition for osteoporosis ie a femoral neck BMD T-score of ≤–2.5SD no significant non-vertebral fracture benefit was observed with Bonviva treatment. It was therefore not surprising that these data were insufficient to support a hip fracture indication and hence why the all encompassing claim 'Bonviva once monthly for postmenopausal osteoporosis' should not be permitted.

The companies agreed with Roche and GlaxoSmithKline that the absence of proof of a statistically significant reduction in the risk for hip fractures did not mean that Bonviva was not effective in relation to hip fractures; just that it had yet to be proven. The companies thus respectfully requested that Roche and GlaxoSmithKline proved this relationship and had their licensed indication modified before they started to make claims on hip fracture efficacy. To do otherwise would open up the opportunities for pharmaceutical companies to claim efficacy in a multitude of indications just because they believed their medicine would show efficacy in such patients if tested.

The companies stated that taking everything into consideration, they were very concerned by Roche's and GlaxoSmithKline's statement: 'In their ruling the Panel "considered that many readers would assume it was a simple choice between once-weekly and once-monthly therapy and that **in all other respects the two medicines were equal**." We would suggest that in terms of the type of patient to be treated and the likely risk/benefit profile then **this was in fact the case**' (emphasis added).

This point of view apparently formed the basis of the Bonviva once-monthly communication. The companies alleged that this was incorrect; regulatory authorities did not consider the medicines' indications to be the same and this was reflected in the differences in the indications of the bisphosphonates. As a result of Roche and GlaxoSmithKline's claims, physicians reading the Bonviva once monthly leavepiece might prescribe Bonviva assuming that it had the same efficacy (ie vertebral and hip fracture reduction) as the weekly bisphosphonates. Consequently certain patients at particular risk of hip fracture might be prescribed the product, which raised concerns for patient safety.

In conclusion the companies agreed with the Panel's ruling that the claim 'Bonviva once-monthly for postmenopausal osteoporosis' in the leavepiece was in breach of Clauses 3.2, 7.2 and 7.4.

APPEAL BOARD RULING

The Appeal Board noted that according to the SPC Bonviva 150mg was indicated for the 'Treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established'.

The Appeal Board noted that the CPMP Note for Guidance on Postmenopausal Osteoporosis in Women, January 2001, in force at the time of the granting of the Bonviva marketing authorization stated 'From the regulatory viewpoint two therapeutic indications are recognised, ie.: prevention of osteoporosis in postmenopausal women … treatment of osteoporosis. The applicant will be requested to study the effect of the investigated drug on both spinal and femoral (not all non-vertebral) fractures …. The indication will be granted only if anti-fracture efficacy has been demonstrated at, at least, one site and no deleterious effect has been shown at the other site. In the "indication" part of the SPC, it will be clearly specified if anti-fracture efficacy has been shown at the spine and/or at the hip. Failure to demonstrate anti-fracture efficacy at the second site will also appear in this section of the SPC'. The Appeal Board considered that the statement, 'Efficacy on femoral neck fractures has not been established' in the indication section of the SPC provided the evidence base for the indication, which was the treatment of PMO.

The Appeal Board noted that the leavepiece at issue referred to Chesnut *et al* (2004) and included a positive claim for the reduction in risk of vertebral fracture. Chesnut *et al* had not been powered to assess hip fracture efficacy. There was no mention of hip fractures in the leavepiece. The Appeal Board considered that the claim 'Bonviva once monthly for postmenopausal osteoporosis', in the context of a comparison of patient preference for Bonviva or alendronate, did not imply that efficacy data was available to show that Bonviva decreased the risk of hip fractures. The comparison was between two bisphosphonates which were both indicated for the treatment of PMO.

The Appeal Board did not consider that the claim, in the context of the page, was sufficient to mislead in relation to the evidence base of the medicine and so it was not inconsistent with the Bonviva SPC. The Appeal Board ruled no breach of Clause 3.2. The Appeal Board considered that the claim was not misleading and could be substantiated and thus ruled no breaches of Clauses 7.2 and 7.4 of the Code. The appeal on this point was successful.

2 Claim 'Faced with 52 or 12 tablets a year, what would patients prefer?' and use of the BALTO (Bonviva Alendronate Trial in Osteoporosis) study to claim patient preference for a monthly bisphosphonate compared with a weekly bisphosphonate

COMPLAINT

Procter & Gamble and Sanofi-Aventis alleged that this statement and the use of the BALTO study to imply patient preference were misleading. Firstly they reinforced the misinterpretation implied by the claim 'Bonviva once-monthly for postmenopausal osteoporosis', since the reader would assume that the efficacy of both weekly and monthly therapies was the same. Secondly, such a study was open to misinterpretation and the results misleading if the patients involved in the study made their choice of preferred therapy assuming that Bonviva and alendronate had the same efficacy. Patients were not explicitly informed about the differences in the licensed indications/efficacy between the two therapies.

The BALTO study (Emkey *et al* 2005) was a 6 month open label study in which patients took alendronate once a week for 12 weeks, then changed to Bonviva once-monthly for 3 months. At the end of the study, of the 93% of patients who expressed a preference 71% stated that they preferred the once-monthly Bonviva regime.

It was therefore irresponsible to make a strong promotional claim that patients preferred a monthly therapy based upon a study that was not robust enough to consider all important influencers of patients' preference and account for those in the study design, specifically in this case to inform the patients of the important clinical differences between the two therapies.

The companies alleged that use of this study to claim a patient preference for Bonviva once-monthly over alendronate once-weekly was misleading and in breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Roche and GlaxoSmithKline explained that the headline 'Faced with 52 or 12 tablets a year, what would patients prefer?' was used to introduce the first once-monthly bisphosphonate for osteoporosis and to highlight a simple, undeniable difference between weekly and monthly medications. It made no claims in itself, but posed an important question that challenged the health professional to consider the impact of dosing regimens on patients. This was particularly pertinent given the mode of administration of bisphosphonates where patients were required to fast for several hours before each dose and remain upright during and after each dose. This headline would be acceptable as a rhetorical question even if there were no study of patient preference and therefore the discussion of the study itself was not relevant here. As such the claim did not breach Clauses 7.2 or 7.3 of the Code.

Patients were enrolled in the BALTO study if the prescriber considered them suitable for either the weekly or monthly medication. Given this inclusion criteria the companies submitted that the use of this study to support the claim was not misleading. Unlike the vast majority of medicines, the administration of bisphosphonates was complex and could be onerous. Compliance with these long-term medicines was poor. This was why the weekly formulations were welcomed by patients and prescribers, so that this inconvenience could be reduced compared to the daily burden. The companies had developed a monthly preparation which was even less burdensome. The BALTO study was a straightforward, randomised, two way cross-over study to evaluate patient preference and convenience for once-monthly ibandronic acid and once-weekly alendronate both of which would be indicated for the treatment of PMO.

No comparative efficacy claims were made. The claim that patients preferred a once-monthly bisphosphonate to a weekly bisphosphonate was clear, fair, unambiguous and not misleading and therefore not in breach of Clauses 7.2 and 7.3 of the Code.

PANEL RULING

The Panel did not consider that the claim 'Patients prefer a monthly to a weekly bisphosphonate' was self evident. Some patients might find it easier to establish a routine of taking a tablet on the same day every week than on the same date every month. The Panel noted that the method of administration of oral bisphosphonates would impact on patients. Fosamax (alendronate) (once weekly) had to be taken at least 30 minutes before the first food, beverage or medicine of the day with plain water only. Patients should not lie down until after their first food of the day which should be at least 30 minutes after taking the tablet. The dosing instructions for Bonviva 150mg were different in that the medicine had to be taken after an overnight fast of at least 6 hours and one hour before the first food, drink (other than water) or medicine of the day. Patients should not lie down for one hour after taking Bonviva.

The Panel noted that the patients in the study had not been informed of the differences in the indications for Bonviva and alendronate. This might have influenced their decision as to which medicine to take. It appeared from the data presented in the leavepiece that the only difference was in the dosing interval and not in the method of administration or indications. In addition given the context of the page readers would assume that alendronate and Bonviva had the same indication and this was not so. The Panel considered that the comparison was unfair and breaches of Clauses 7.2 and 7.3 of the Code were ruled.

APPEAL BY ROCHE AND GLAXOSMITHKLINE

Roche and GlaxoSmithKline submitted that the Panel's ruling was based upon its interpretation of Bonviva's licence and that this reflected a difference in the indications between Bonviva and alendronate. Given the evidence already presented that Bonviva was licensed for the treatment of PMO and patients were included on the basis that clinicians considered them suitable for either treatment as part of the inclusion criteria, and given that the study was specifically and robustly designed to consider patient preference, this claim was accurate, balanced, fair, objective and unambiguous and should not be ruled in breach.

The companies submitted however that in future they would include a statement clarifying the difference in the method of administration of the two products when referring to BALTO data and a statement that patients involved in this study were all PMO patients who were deemed suitable for both treatments.

The companies explained that the BALTO study was an open label, randomised, two way cross-over study. PMO patients were randomised to once monthly ibandronic acid for 3 months followed by once weekly alendronate for 12 weeks (sequence A) or once weekly alendronate for 12 weeks followed by once monthly ibandronic acid for 3 months (sequence B).

The companies submitted that no attempt was made by clinicians or patients to assess efficacy and no efficacy claims were made on the basis of this study. As in standard clinical practice, the clinicians ensured the patients were suitable for either medicine under test. Both medicines were considered by the regulatory authorities to be possible first line treatments for PMO. As was true for most medicines within a therapeutic category, there were differences in the evidence base for each product. If two products were licensed for the same disease (osteoporosis), the same target population (postmenopausal women) and were both possible first line treatments then it was not unreasonable to expect some doctors to prescribe one and some the other, given the same patients in front of them. There was no data to definitively show that one was significantly better than the other as no head to head comparisons had been done. It would be unreasonable to expect a clinician to discuss all clinical study outcomes with each patient before prescribing a medicine. Without a head to head comparison it was very difficult for clinicians let alone patients to make an informed decision on which product was likely to be more effective than the other, and both were licensed first line treatments for the disease that the patient suffered. Compliance with long term medication in general was poor. On top of this, the dosing requirements for all bisphosphonates were onerous and impacted further on compliance. The Panel listed a number of differences in dosing requirements, but the only difference between Bonviva and the other bisphosphonates in this respect was that the post-dose requirement to fast and stay upright was an hour rather than 30 minutes. All other requirements were identical although Bonviva was more explicit in the duration of the pre-dose fast (6 hours) whereas Fosamax referred to 'after getting up for the day and before the first food, beverage, or medicinal product of the day'. In practice this was after an overnight fast which was likely to be at least 6 hours. All patients took the medicines according to their licences, ie after an overnight fast and remained standing or sitting erect for 30 minutes in the case of alendronate and 60 minutes in the case of Bonviva. Thus the patients all had true to life experience of taking either alendronate weekly or Bonviva monthly. The only claims made with regards to this study were based purely on patient preference for one treatment regime over another. As such the companies appealed the Panel's ruling of a breach of Clauses 7.2 and 7.3.

The companies hoped given the further clarification on the wording of the licence and the intention of the EMEA in granting the licence, the clinical impossibility of identifying patients only at risk of vertebral fracture, and their agreement to include more detail in the prescribing information and on the details of the BALTO study, that the Appeal Board would consider their appeal favourably.

COMMENTS FROM PROCTER & GAMBLE AND SANOFI-AVENTIS

Procter & Gamble and Sanofi-Aventis noted that

Roche and GlaxoSmithKline had stated that both Bonviva and Fosamax were considered by the regulatory authorities to be possible first line treatments for PMO; there was no justification for this statement. The regulatory authorities had made no such claim on behalf of Bonviva, or any other osteoporosis medicine. The National Institute for Health and Clinical Excellence (NICE) had begun a review of osteoporosis medicines, the draft conclusion of which was that the bisphosphonates, alendronate (Fosamax), risedronate (Actonel) and etidronate (Didronel PMO) were recommended as first line therapies. Nowhere in any of the text was ibandronate (Bonviva) mentioned.

Procter & Gamble and Sanofi-Aventis noted that Roche and GlaxoSmithKline had agreed to include a statement clarifying the differences in the methods of administration of the two products when referring to the BALTO study (2005). However, this did not address the fundamental issue that the study was not performed appropriately. When conducting market research it was imperative that the patients were properly and completely informed so they could make a meaningful decision. It appeared from the information provided that patients were not properly informed in the patient consent/information sheet used in the BALTO study.

The companies noted that Roche and GlaxoSmithKline had submitted that it would be unreasonable to expect a clinician to discuss all clinical study outcomes with each patient before prescribing a medicine. However, this was not necessary for a study like BALTO, since for a simple study of this nature, the licensed indications and dosing regimens could easily be covered in the patient information. Another patient preference study had recently been completed, and would be presented at the next international congress on osteoporosis (ECCEO March 2006, Vienna). In this study the patients were informed of key differences including fracture efficacy between Bonviva once-monthly and Actonel once a week. Interestingly, the results directly contradicted those of the BALTO study showing that when all the important differences were considered, patients preferred a weekly therapy. In summary, the companies agreed with the Panel's ruling that the use of the claim in question and the BALTO study in the Bonviva once-monthly promotional leavepiece was in breach of Clauses 7.2 and 7.3.

APPEAL BOARD RULING

The Appeal Board noted that the BALTO preference study was started before the marketing authorization for Bonviva had been granted and thus before the evidence base for the product was fully assessed. Patients could not have known that, in contrast to alendronate, efficacy on hip fractures would not be established for Bonviva. In that regard the patients did not have the full facts about Bonviva and thus, in the Appeal Board's view, would not have been able to express a genuine, well informed preference between it and alendronate. In that regard the Appeal Board considered that the comparison was unfair and was not based on an up-to-date evaluation of all the evidence. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.3 of the Code. The appeal on this point was unsuccessful.

During its consideration of this case the Appeal Board was extremely concerned about the omission of the statement 'Efficacy on femoral neck fractures had not been established' from the indication section of the prescribing information. It considered that all the information about the indication should have been given; a significant piece of information had been omitted. This was wholly unacceptable. The Appeal Board noted that this point had been raised by the Panel and that Roche and GlaxoSmithKline had accepted the Panel's recommendation in this regard. Nonetheless the Appeal Board requested that Roche and GlaxoSmithKline be advised of its views.

Complaint received **8 November 2005**

Case completed **10 April 2006**

CONSULTANT NEUROLOGIST v ALLIANCE

Symmetrel leaflet

A consultant neurologist complained about a Symmetrel (amantadine) leaflet issued by Alliance. In a previous case, Case AUTH/1749/8/05, the complainant had noted that the leaflet was headed 'Are psychotic phenomena in PD [Parkinson's Disease] drug related?'. Beneath the heading was a reference to a study which suggested that psychotic phenomena in Parkinson's disease were not drug related (Merims *et al* 2004). The complainant had alleged that the leaflet was misleading; in the case now at issue he further alleged that the leaflet represented a serious breach of the Code.

The complainant stated that there was overwhelming published evidence that medicines used in Parkinson's disease precipitated hallucinations illustrated by the inclusion of hallucinations as side-effects in all summaries of product characteristics (SPCs) for dopaminergic agonists. There was also a large body of published evidence discussing psychosis in Parkinson's disease that highlighted the role of medicines. None of this was mentioned in the leaflet at issue. All clinicians knew and accepted that pharmaceutical promotional material was biased. The complainant submitted, however, that he had complained because he considered the leaflet was seriously misleading, ie that it could result in avoidable morbidity in patients with Parkinson's disease. As such he feared it represented a serious breach of the Code.

No-one had suggested that medicines alone were the cause of hallucinosis in Parkinson's disease. This was obvious from the observation that dopaminergic agonists used in patients without Parkinson's disease rarely caused hallucinations, but that they did so commonly in patients with Parkinson's disease and the risk increased as the disease advanced. There was a complex interaction between the brain disorder and the medicine. However, to suggest that the medicines were not causative was dangerous. The complainant noted that non-experts often sub-optimally managed hallucinosis in Parkinson's disease and the material at issue could only worsen this problem.

The Panel noted that in Case AUTH/1749/8/05 it had considered that the leaflet implied that anti-Parkinson medicines had no role in the development of hallucinations. In that regard the Panel had noted that hallucinations were listed as an occasional (1-10%) adverse effect of Symmetrel therapy. The Panel considered that the leaflet was misleading and had ruled a breach of the Code which was accepted by Alliance. The complainant had subsequently alleged that the use of the material should be regarded as a serious breach of the Code and Alliance had now been asked to respond to the allegations in relation to the requirements of Clause 2 which had not been at issue in the previous case.

The Panel considered that its ruling in Case AUTH/1749/8/05 was relevant. The leaflet implied that Parkinson's disease medicines had no role in the development of hallucinations and that was not so. The Panel considered that this was a serious matter and noted that the complainant had been moved to submit a second complaint about the item. Nonetheless the Panel did not consider that the matter was sufficiently serious such that it warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure.

A consultant neurologist complained about a leaflet (ref AL/467/03.05/2.5a) for Symmetrel (amantadine) issued by Alliance Pharmaceuticals Ltd. The leaflet was signed by a business unit manager and had been sent to neurologists and care of the elderly physicians.

The complainant had previously complained about the leaflet, Case AUTH/1749/8/05, wherein a breach of Clause 7.2 was ruled. In Case AUTH/1749/8/05 the complainant had noted that the leaflet was headed 'Are psychotic phenomena in PD [Parkinson's Disease] drug related?'. Beneath the heading was a reference to a study which suggested that psychotic phenomena in Parkinson's disease were not drug related (Merims *et al* 2004). In Case AUTH/1749/8/05 the complainant had alleged that the leaflet was misleading; in the case now at issue, Case AUTH/1781/11/05, he further alleged that the leaflet represented a serious breach of the Code.

COMPLAINT

The complainant stated that there was overwhelming published evidence that medicines used in Parkinson's disease precipitated hallucinations. This was, for example, illustrated by the inclusion of hallucinations as side-effects in all summaries of product characteristics (SPCs) for dopaminergic agonists. There was also a large body of published evidence discussing psychosis in Parkinson's disease that highlighted the role of medicines. None of this was mentioned in the leaflet at issue. All clinicians were aware and accepted that pharmaceutical promotional material was biased. The complainant submitted, however, that he had complained because he considered the leaflet was seriously misleading, ie that it could result in avoidable morbidity in patients with Parkinson's disease. As such he feared it represented a serious breach of the Code.

No-one had ever suggested that medicines alone were the cause of hallucinosis in Parkinson's disease. This was obvious from the observation that dopaminergic agonists used in patients without Parkinson's disease rarely caused hallucinations, but that they did so commonly in patients with Parkinson's disease and the risk increased as the disease advanced. There was a complex interaction between the brain disorder and the medicine. However, to suggest that the medicines were not causative was dangerous.

The complainant noted that in its response to Case AUTH/1749/8/05, Alliance had stated that the purpose of the leaflet was to question the widespread belief that psychotic phenomena were always medicine-related in Parkinson's disease. Whether that was its intention or not, the leaflet clearly asked 'Are

psychotic phenomena in PD drug related?' not 'Are psychotic phenomena in PD *always* drug related?'. Thus Alliance suggested that there was a question of any role of any medicine in precipitating psychosis in Parkinson's disease, a claim that was grossly misleading. The second headline read 'No evidence for drug-related hallucinations'. This again was grossly misleading, as it referred to the conclusions of only one study and ignored even the SPC information in the public domain, let alone what was in peer reviewed journals.

The complainant noted that medicine-induced hallucinosis in Parkinson's disease was a major and challenging clinical problem. In the complainant's hospital alone there were two or three in-patients suffering these severe side-effects at any time, and there were many more patients in the community whose medication had to be carefully managed to reduce this unpleasant and potentially life-threatening common adverse effect of drug treatment. Severe dopaminergic drug-induced paranoid states were all too common, as were patients who became violent and dangerous under the influence of such medicines. Non-experts often sub-optimally managed hallucinosis in Parkinson's disease and Alliance's promotional material could only worsen this problem. If promotional material that was potentially dangerous did not represent a serious breach of the Code, then what did?

The complainant could not accept that it was appropriate for promotional material to present published data in a dangerous, unbalanced and biased way. Those reading this material were in no position to assess the validity of Merims *et al* in the context of the whole body of evidence on the subject. The pharmaceutical industry should be censured firmly when it picked and chose published material to make a case in favour of its medicine. When this produced a definite risk to the safety of patients it must be considered a serious breach of the Code.

When writing to Alliance the Authority asked it to respond in relation to Clause 2 of the Code.

RESPONSE

Alliance stated that the leaflet questioned the widespread belief that psychotic phenomena, including hallucinations, in Parkinson's disease patients were always drug-related by reporting the observations from a retrospective case review, Merims *et al*. Merims *et al* compared the profiles of Parkinson's disease patients with hallucinations (n=90) with Parkinson's disease patients without hallucinations (n=332). A Cox proportional hazards model was used to identify associations between the risk of developing hallucinations and disease variables, such as age at first diagnosis, and l-dopa adjunctive therapies. Hazard ratios were calculated for all these variables.

For l-dopa adjunctive therapies (n=348), including amantadine, hazard ratios were all found to be approximately 1 and were not statistically significant ($p>0.05$). Merims *et al* therefore concluded that none of the agents commonly used as an adjunct to l-dopa therapy in Parkinson's disease constituted an additional risk for developing hallucinations. When hazard ratios were calculated for the presence of dementia and the age of onset of motor symptoms, they were found to be significantly related to the risk of developing hallucinations.

Alliance stated that an additional retrospective study on the incidence of visual hallucinations in Parkinson's disease had since been published and this further questioned the misconception that hallucinations were always drug-related (Williams and Lees). In this study, the records of 788 patients with Parkinsonism (diagnosed before death and confirmed pathologically at post mortem), including idiopathic Parkinson's disease, were assessed for reports of visual hallucinations, although only 744 cases were assessed for this study. Of these 744 cases, there were 445 with Parkinson's disease and 44 with dementia with Lewy bodies (n-489), these two groups were combined for the analysis. Of this group, 253 (52%) were recorded as having experienced visual hallucinations. Factors affecting the onset of visual hallucinations, including age of onset of Parkinsonism, medicines used, maximum dose of l-dopa, were investigated.

Statistical analysis including a Cox regression analysis (for early clinical features that could be predictive of the development of visual hallucinations) and the calculation of Spearman's correlation (time to onset of visual hallucinations after initiation of drug therapy) were performed.

In patients with Parkinson's disease, the onset of visual hallucinations typically occurred in the second half of the disease course and were associated with other clinical features including cognitive dysfunction, early axial rigidity and age of onset of Parkinson's disease. When the association with drug therapy and visual hallucinations were examined, they were found to be weakly correlated with the use of selegiline (Spearman's correlation coefficient 0.22, $p=0.005$) but not to the use of other medicines including l-dopa, anticholinergics and amantadine.

Draft clinical guidelines on the management of Parkinson's disease recommended that when psychosis developed, the initial treatment should include a general medical assessment with consideration being given to withdrawal of medicine which might have triggered the psychotic episodes (Section 9.42. Parkinson's Disease, Diagnosis and Management in Primary and Secondary Care. Draft for first consultation. NICE August 2005).

There was no doubt that anti-Parkinson's mediations could cause hallucinations. This was an adverse effect widely recognised by neurologists and others managing patients with Parkinson's disease. It was listed in the SPC for several agents including Symmetrel. What Merims *et al*, Williams and Lees and the draft NICE guidelines highlighted was that the development of psychosis in a patient should not automatically be assumed to be an adverse effect to the patient's medicine(s). Questioning the link between a patient's medicine and his hallucinations was not misleading, was not potentially dangerous and might result in the more effective use of anti-Parkinson's disease medicines.

Merims *et al* and Williams and Lees were reports of retrospective case reviews. Whilst such a study design was not at the top of the hierarchy of clinical evidence, both papers clearly described their methodologies and statistical methods. The conclusions of such a study were not definitive but were indicative. In the introduction to the paper, Merims *et al* reviewed previous work which also suggested that the link between psychotic phenomena in Parkinson's disease and anti-Parkinson's disease medicine was not necessarily direct. They further referred to an unpublished study which suggested that there might be a genetic factor. The evidence, whilst limited, legitimately questioned the link between the development of hallucinations and anti-Parkinson's disease medicine.

Alliance explained that the leaflet in question was sent out to neurologists and care of the elderly physicians in the UK. The target audience was prescribers working in the area of movement disorders including Parkinson's disease. These were not 'non-experts' and were highly unlikely to change their management of hallucinations in patients with Parkinson's disease based solely on a pharmaceutical company produced promotional mailing. Alliance did not consider that the leaflet item in question had resulted in any serious, avoidable morbidity in any patient with Parkinson's disease and denied a breach of Clause 2 of the Code.

'Are psychotic phenomena in PD drug related?' was not a claim but a question. Furthermore, it was neither inaccurate nor misleading based on the observations of Merims *et al* and Williams and Lees.

PANEL RULING

The Panel noted that Alliance had accepted the Code of Practice Panel's ruling in Case AUTH/1749/8/05 that the leaflet was misleading, in breach of Clause 7.2 of the Code. The complainant had subsequently alleged that the use of the material should be regarded as a serious breach of the Code and Alliance had now been asked to respond to the allegations in relation to the requirements of Clause 2.

Relevant part of the Panel Ruling in Case AUTH/1749/8/05

The Panel noted that the heading of the leaflet 'Are psychotic phenomena in Parkinson's disease drug related' was followed by the following:

> 'It is commonly assumed that psychotic phenomena like hallucinations in Parkinson's disease (PD) are drug related. However, it is important to clarify whether this supposition is an accurate one. A recent study used a Cox proportional hazards model to assess the medical records of 422 PD patients – in order to ascertain whether their drug profile was related to the presence of hallucinations.' This statement was referenced to Merims *et al*.

A second heading stated 'No evidence for drug-related hallucinations' beneath which it was explained that Merims *et al* found no correlation between a patient's drug profile and the development of hallucinations. It was stated that daily l-dopa was not significantly different in patients with hallucinations compared with those who had never experienced hallucinations. Age at onset of motor symptoms as well as presence of dementia were identified as definitive risk factors for hallucinations. It was stated that in the light of such clinical data, it would seem reasonable that patients' medical therapy was not delayed, reduced or adjusted.

The Panel noted that the objective of Merims *et al* was to determine the contribution of anti-Parkinson medicines to the development of hallucinations in patients with Parkinson's disease. The authors confirmed that psychotic phenomena were not related simply to drug treatment but that other intrinsic factors might play a role.

The Panel considered, however, that the leaflet implied that anti-Parkinson medicines had no role in the development of hallucinations. In that regard the Panel noted that hallucinations were listed as an occasional (1-10%) adverse effect of Symmetrel therapy. The Panel considered that the leaflet was misleading in that regard. A breach of Clause 7.2 was ruled.

Panel Ruling in Case AUTH/1781/11/05

The Panel noted that in the present case the complainant had alleged that the promotional leaflet was potentially dangerous and a serious breach of the Code. Alliance had thus been asked to respond in relation to the requirements of Clause 2, which had not been at issue in the previous case.

The Panel considered that its ruling in Case AUTH/1749/8/05 was relevant. The leaflet implied that Parkinson's disease medicines had no role in the development of hallucinations and that was not so. The Panel considered that this was a serious matter and noted that the complainant had been moved to submit a second complaint about the item. Nonetheless the Panel did not consider that the matter was sufficiently serious such that it warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure.

Complaint received **14 November 2005**

Case completed **11 January 2006**

GENERAL PRACTITIONER v SERVIER

Arrangements for a meeting

A general practitioner complained about a meeting for health professionals held by Servier on Friday/Saturday, 11/12 November, at a hotel in Glasgow. The complainant asserted that the hospitality was excessive and that an overnight stay was unnecessary for such a short programme on a narrow topic. He considered that the hospitality was the primary inducement for attendance. He was further concerned by the amount of alcohol consumed on a Friday night.

The complainant was also concerned that this was direct promotion of one study, the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT), rather than a review of hypertension and therefore the meeting might not meet the high educational standards expected.

The Panel noted that the Glasgow meeting was one of a series of six regional GP symposia on the management of hypertension following the publication of the ASCOT results. Although many of the attendees at the meeting were relatively local some came from much further afield eg Aberdeen. The meeting was the only one of its kind to be held in Scotland. According to the agenda the meeting started at 7pm on Friday evening and lasted, that night, until 10.30pm including $2^1/_2$ hours for dinner and a quiz. The educational sessions began again at 8.30am on Saturday morning and the meeting finished at 12.30-1pm followed by lunch. The invitation to the meeting stated that overnight accommodation was available if the delegate did not live locally. The Panel noted that 24 out of 27 delegates stayed overnight. Nonetheless, on balance, the Panel did not consider that an overnight stay was unreasonable; delegates to the meeting were drawn from a wide geographical area.

The agenda showed that on Friday evening there was to be an hour of education – half an hour examining the importance of ASCOT followed by half an hour of questions and answers. Servier had submitted that the medical challenge and case studies to be completed over dinner would take about half an hour. There was four to four and a half hours of education on the Saturday. The meeting thus comprised five and a half to six hours of education.

The cost of accommodation was £150 which was the 24 hour delegate rate and included dinner, breakfast and lunch. The cost of drinks on the Friday night was approximately £21.50 per head. The Panel queried whether £171.50 was in line with what the delegates would have paid for themselves.

The Panel considered that the arrangements for the meeting were on the limits of acceptability. Servier had offered overnight accommodation at a four star hotel in association with no more than six hours of education. In the Panel's view the meeting could have been held over one day with no overnight accommodation. Delegates were, however, drawn from a wide area and the timing of the meeting meant that attendees had ample opportunity to talk to one of the key investigators of ASCOT. On balance the Panel did not consider that the hospitality offered would be viewed as the primary inducement to attend the meeting. No breach of the Code was ruled.

The Panel did not consider that the amount of alcohol consumed was excessive. The amount of wine available before and during dinner had been controlled and the after dinner bar bill was modest considering the number of delegates. No breach of the Code was ruled.

With regard to the content of the meeting, all of the presentations were about ASCOT – this was made clear in the invitation/agenda. The Panel did not consider it inappropriate to hold a meeting on just one topic and in that regard ruled no breach of the Code.

Overall the Panel did not consider that the arrangements for the meeting were such as to bring the industry into disrepute. No breach of Clause 2 was ruled.

A general practitioner complained about a meeting for health professionals held by Servier Laboratories Ltd on Friday/Saturday, 11/12 November 2005 at a hotel in Glasgow. A copy of the invitation/agenda was provided. The meeting was entitled 'Clear Thinking in Hypertension' and, according to the agenda, started on the Friday evening at 7pm; the formal part of the evening, including dinner during which there was a medical challenge quiz, ended at 10.30pm. On the Saturday morning presentations started again at 8.30am and the meeting ended at 12.30-1pm.

COMPLAINT

The complainant asserted that the hospitality was excessive and that an overnight stay was unnecessary for such a short programme on a narrow topic. He considered that the hospitality was the primary inducement for attendance. The complainant was further concerned by the amount of alcohol consumed on a Friday night and suggested that the personal business accounts of attending representatives might also contain related expenses.

The complainant was also concerned that this was direct promotion of one study, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), by Servier rather than a review of hypertension and therefore the meeting might not meet the high educational standards expected.

RESPONSE

Servier explained that the Glasgow meeting was one of a series entitled 'Clear thinking in hypertension management' that was based on ASCOT. The meeting was of high significance and importance to the daily clinical practice of the delegates and had a high educational standard.

Servier explained that the benefits of antihypertensives for the prevention of cardiovascular

mortality and morbidity were well established, however, no individual trial had shown a significant reduction in coronary heart disease (CHD) events. Data on the relative effects of newer antihypertensives compared with standard treatment options, especially in combination treatment regimens was very limited. Which antihypertensives should be used first-line had been the subject of debate and controversy for many years. To reach blood pressure targets recommended in national and international guidelines, two or more antihypertensives were needed for most patients. There was no clinical trial evidence for the optimum combinations of antihypertensives. ASCOT was set up to address the question of which combination was better, 'old' or 'new'.

ASCOT was stopped more than a year early, in November 2004, due to the reduction of all-cause and cardiovascular mortality in the amlodopine ± perindopril arm compared to the atenolol ± bendroflumethiazide arm. The results demonstrated categorically that treating hypertensives with amlodopine ± perindopril saved significantly more lives compared with treating patients with atenolol ± bendroflumethiazide. The trial was a landmark study that would have a significant impact on UK clinical practice and therefore had enormous potential implications for GPs who treated and managed the majority of hypertensives. The impact and importance of the trial could not be overstated. Over 9,000 of the ASCOT patients were based in the UK and the trial used four medicines that were among the top ten most widely prescribed antihypertensives in the UK – atenolol and bendroflumethiazide were the two most widely prescribed antihypertensives. The relevance of ASCOT to UK practice was also reflected by the fact that within days of the data release both the National Institute for Clinical Excellence (NICE) and the British Hypertension Society (BHS) agreed that they would review their hypertension guidelines to take the results into account – a new joint NICE/BHS guideline for hypertension was anticipated in Spring 2006.

Servier explained that in November 2004 it discussed a proposal to hold six regional meetings, under the banner of the British Journal of Cardiology and supported by an educational grant from Servier, to communicate details of ASCOT and the results and implications for the treatment of hypertension. Servier consulted two clinical experts about the best way to do this and it was decided that it would be most beneficial if each meeting was chaired by an investigator from ASCOT and co-chaired by someone local with a high professional standing within cardiology and hypertension management. It was decided that the other speakers at each meeting should also be leaders in the area of hypertension management.

As the results from ASCOT would clearly have implications for the future management of hypertension and all relevant guidelines, the meetings were entitled 'Clear Thinking in hypertension management' and it was made clear that the meetings were about the ASCOT results and the possible implications of these in general practice. As the implications were focussed on general practice it was thought most appropriate to target the meeting series to GPs, aiming for approximately 100 delegates at each meeting.

Servier booked venues in Birmingham, London, Glasgow, Bristol, Newcastle and Manchester which had private and separate meeting rooms and private dining areas large enough for 100 people; they also had enough rooms for overnight stays. The venues were selected on price, appropriate facilities and suitability. Apart from the logistical aspects of the venues appropriate for these meetings, ensuring that they met the requirements of the Code was fundamental to their selection.

Servier stated that an initial mailing was sent out in July 2005 to 15,529 GPs, 680 primary care organisation cardiologists/other health professionals, 170 disease leads and 514 pharmacy advisors. Responses were to be sent back to Servier's meetings department. The initial invitation was sent to a large number of primary care health professionals in order to get a sufficient number of attendees at each venue. When a venue became fully subscribed delegates would be offered a place at other locations that had vacancies. To offer flexibility in terms of dates, applicants were able to select the date, and hence venue of their choice, but no travel expenses were offered.

A letter of confirmation containing 'house-keeping' details of the hotel, meeting agenda and location map and directions was then sent.

An advertisement appeared in the British Journal of Cardiology advertising the meeting series in July/August 2005.

After consultation with the two clinical experts the meeting agenda was considered very carefully so that it fulfilled the objectives of the meeting and met the requirements and expectations of the attendees. The main purpose of the meeting was to tell attendees about the ASCOT results, put these into context according to other large clinical studies in hypertension, have open discussions about hypertension management and how ASCOT could potentially influence future hypertension management.

Having a lead investigator from ASCOT presenting the importance of the trial and then being part of panel discussions and question and answer sessions was a deliberate and important part of the meeting; it meant that the person best qualified to answer any questions and discussion points was present at the meeting. The meeting organisers regarded this as a distinct benefit for the attendees.

The meeting agenda was also specifically structured after much discussion and consultation as to the best and most appropriate way of communicating the results of ASCOT, the potential implications of ASCOT for hypertension management in practice, hypertension management and hypertension guidelines in general and allowing the opportunity for questions and open discussion thus fulfilling the objectives of the meeting.

The ASCOT investigator would open the meeting and give an outline of the importance of ASCOT. This presentation was designed to give brief details of the

rationale and objectives behind ASCOT: study design, patient inclusion criteria, key results, details of adverse events, conclusions and possible implications of the study. As the remainder of the meeting's presentations, questions and discussions were likely to be predominantly based on ASCOT, or at least be asked/discussed with it in mind, it was important that attendees had a clear understanding of the study from one of the most appropriately qualified people to give it.

The first two questions of the medical challenge quiz were general knowledge, the next five were directly related to ASCOT and the final three related to hypertension guidelines. The quiz was to encourage discussion between the attendees as this was one of the objectives for the following day. It was also designed to be a 'memory jogger' about facts and figures presented earlier by the ASCOT investigator and finally to include questions about hypertension guidelines as this was the context in which ASCOT was being discussed.

Also during dinner a case study was handed out to each table to generate discussion about hypertension management in individual patients that might be encountered in general practice. The case studies were discussed and completed at table and then presented to the meeting the following day by a nominated person from the table.

On the Saturday morning there were three and a half hours of planned meeting content. There was a short introduction by the chairman followed by a fifty-minute presentation 'The ASCOT drugs – getting the right combination'. There were then two half hour presentations 'The need for change in hypertension management' and 'ASCOT in perspective'. After a coffee break there was one and a half hours of facilitated discussion with the speakers forming the panel.

With regard to the selection of invitees to the meeting in Glasgow, Servier explained that after the initial mailing and the advertisement in the British Journal of Cardiology about the meetings there was still a number of places available in Glasgow and so further mailings were sent, in September 2005, to 1728, and later to 2698, local health professionals. Servier provided a list of attendees. Delegates had to sign a registration document for both the Friday and Saturday sessions. There were 27 delegates with 24 staying at the hotel on Friday night. There were also seven Servier employees, five speakers, one audiovisual technician and one member from a medical communications consultancy at the meeting and staying overnight. Therefore 38 people were present on the Friday evening and stayed overnight. Attendees travelled from Edinburgh, Inverness, Aberdeen, Cumbria, Glenrothes and Irvine. Speakers were relatively local to the meeting but the chairman lived in London.

Servier stated that the agenda for the Glasgow meeting closely followed the scheduled agenda as described above and was chaired by an ASCOT investigator. The winners of the quiz nominated a Scottish medical charity to be awarded the prize. Members of the winning table did not personally receive any prize. The case studies were discussed and completed towards the end of dinner and then discussed as part of the facilitated panel discussion the following day. On the Saturday the meeting again closely followed the planned agenda. There was a high level of discussion at the facilitated panel session at the end of the meeting and thus the meeting ended a little later than planned.

Servier stated that the speakers' honoraria and expenses were £6321.80. Details of charges from the hotel were provided but in summary were: accommodation £5192; room rental £1200; bar charges £929.10; taxis £105.80 and photocopies £8. A further breakdown of the bar charges was as follows: pre-dinner drinks £126.75, dinner drinks £545.75, after dinner bar (including soft drinks and coffee) £211.80 and piano bar £28.30.

The intention was that attendees would have a glass of sparkling wine before dinner then a maximum of half a bottle of wine per person with dinner. There were five tables of eight people in the dining room. Two bottles of red and two bottles of white wine were opened for each table. A further six bottles of red wine were requested and opened during dinner. Therefore Servier was charged for 26 bottles of wine that were opened. There was no way of knowing exactly how much wine was consumed during dinner but after interviewing Servier representatives present at the meeting they all reported that no one drank excessively. Dinner ended at approximately 11pm. Most delegates went to bed at this time with a few adjourning to the bar. No one was drinking excessively and no one missed the start of the meeting at 8.30am the following morning or left the meeting early.

Meals (Friday night dinner and Saturday lunch) were included in the 24hr rate of £150 per person or £180 per couple. There were four double rooms booked (husband and wife delegates). The spouses were also health professionals to which this meeting was relevant and therefore delegates in their own right.

The lunch on the Saturday was not intended as part of the meeting as demonstrated by the meeting agenda. Lunch was available to delegates however, as it was part of the 24hr rate package from the hotel. Lunch consisted of a two-course buffet.

Apart from travelling expenses from one Servier employee (£37 taxi fares) no other expenses were either charged to hotel rooms or put on Servier representatives' personal expenses.

No travelling expenses were paid to delegates.

Each delegate was given a pack containing: the meeting folder; agenda; chairman and speaker biographies; the importance of ASCOT slides; summaries of presentations from the Saturday session and evaluation questionnaire. The only other material provided to attendees was confirmation of attendance letters, details about the hotel and directions.

Delegates were asked to complete a short evaluation form assessing the presentations, the venue, take-home messages and the overall meeting. Twenty-four delegates completed the evaluation form with the majority rating the value of each presentation as 4 out

of 5 (with 5 being excellent and 1 being poor). A number of evaluations criticised poor standards at the hotel.

It was clear from the scores on the delegate evaluation forms that the delegates rated this meeting as highly educational and of high value.

The facilitated panel discussion on the Saturday demonstrated that: the meeting was of a high educational standard as dictated by the speaker panel; the meeting generated a high level of discussion (one of its prime objectives) on a very broad range of topics related to hypertension management in primary care; the discussion was not restricted to promotion of any particular product or company; the length and detail contained in this one session was indicative of the quality and quantity of the remainder of the meeting and the length and detail of discussion involved in completing the case studies.

Servier stated that it would not have been possible to achieve the objectives of this meeting if it were held on one day. The content would have been too long, the distance travelled by a significant number of delegates would have been impractical and there would not have been the same high level of discussion facilitated by the medical challenge quiz and the case studies completed on the Friday evening. Therefore an overnight stay was justified for this meeting.

Servier disagreed that the programme was short and on a narrow topic. As described previously ASCOT was an extremely important trial in relation to hypertension management with national guidelines being reviewed as a result. The implications of hypertension on health were extensive as were the treatments and treatment strategies available. Many aspects of hypertension management were discussed in some considerable detail during the meeting.

Servier considered that it was clear that the hospitality was not excessive and therefore was not the primary inducement to attend. Servier noted that it had already decided not to use the hotel for future meetings due to its extremely poor standard.

Servier considered that it was clear that alcohol consumption on Friday night was not excessive and was at an appropriate level; reasonable steps had been taken to avoid excessive consumption. No one consumed alcohol to excess on the Friday night, missed the meeting the following morning, left early or missed any of the sessions. Finally, the hotel invoice clearly showed the alcohol Servier had been charged for. There were no other expenses on Servier employee personal expenses in relation to this meeting, all meeting expenses were clearly visible on the hotel invoice.

The presentation slides from the speakers, the transcript of the facilitated discussion, the case studies and the delegate feed back all showed that this meeting was of high educational content fulfilling its objectives.

The structured design of this meeting and quality and quantity of the content clearly demonstrated that this meeting was of a high educational standard in the area of hypertension management. It was clearly not promotion of one product or one company. The location of the meeting in relation to the delegates and speakers together with the large content also made an overnight stay a practical necessity. Evidence provided also demonstrated that the level of hospitality provided was appropriate and in no way excessive or the primary inducement for attendance.

Servier therefore denied that this meeting was in any respect in breach of the Code.

PANEL RULING

The Panel noted that the Authority had not cited those clauses of the Code which Servier should bear in mind in its response. Nonetheless the Panel considered Servier had responded in relation to the substance of Clauses 19.1 and decided to rule on this basis.

The Panel noted that Clause 19.1 of the Code permitted companies to provide appropriate hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings. Hospitality must be secondary to the purpose of the meeting and the level of hospitality offered must be appropriate and not out of proportion to the occasion. The costs incurred must not exceed the level which recipients would normally adopt if paying for themselves. It must not extend beyond members of the health professions or appropriate administrative staff. The supplementary information stated that the impression created by the arrangements must be borne in mind.

The Panel noted that the meeting in Glasgow was one of a series of six regional GP symposia on the management of hypertension following the publication of the ASCOT results. Although many of the attendees at the meeting were relatively local some came from much further afield eg Aberdeen. The Glasgow meeting was the only one of its kind to be held in Scotland. According to the agenda the meeting started at 7pm on Friday evening and lasted, that night, until 10.30pm including $2^1/_2$ hours for dinner and the quiz. The educational sessions began again at 8.30am on the Saturday morning and the meeting finished at 12.30-1pm followed by lunch. The invitation to the meeting stated that accommodation was available if the delegate did not live locally and needed to stay overnight. The Panel noted that 24 out of 27 delegates stayed overnight at the Glasgow meeting. Nonetheless, on balance, the Panel did not consider that an overnight stay was unreasonable; delegates to the meeting were drawn from a wide geographical area.

The agenda showed that on Friday evening there was to be an hour of education – a half hour session examining the importance of ASCOT followed by half an hour of questions and answers. Servier had submitted that the medical challenge and case studies to be completed over dinner would take about half an hour. There was four to four and a half hours of education on the Saturday. The meeting thus comprised five and a half to six hours of education.

The cost of accommodation was £150 which was the 24 hour delegate rate and included dinner, breakfast

and lunch. The cost of pre-dinner drinks (white sparkling wine), dinner drinks (red and white wine) and after dinner drinks was £884.05 or approximately £21.50 per head. The Panel queried whether £171.50 was in line with what the delegates would have paid for themselves.

The Panel considered that the arrangements for the meeting were on the limits of acceptability. Servier had offered overnight accommodation at a four star hotel in association with no more than 6 hours of education. In the Panel's view this could have been held over one day without the need for overnight accommodation. Delegates were, however, drawn from a wide area and the timing of the meeting meant that attendees had ample opportunity to talk to one of the key investigators of ASCOT. On balance the Panel did not consider that the hospitality offered would be viewed as the primary inducement to attend the meeting. No breach of Clause 19.1 was ruled.

The Panel did not consider that the amount of alcohol consumed was excessive. The amount of wine available before and during dinner had been controlled and the after dinner bar bill was modest considering the number of delegates. No breach of Clause 19.1 was ruled.

With regard to the content of the meeting, all of the presentations were about ASCOT – this was made clear in the invitation/agenda. The Panel did not consider it inappropriate to hold a meeting on just one topic and in that regard ruled no breach of Clause 19.1 of the Code.

Overall the Panel did not consider that the arrangements for the meeting were such as to bring the industry into disrepute. No breach of Clause 2 was ruled.

During its consideration of this case the Panel noted that some of the documentation for the meeting jointly featured The British Journal of Cardiology logo and the Servier logo together with the statement 'Supported by an educational grant from Servier Laboratories'. The Panel was concerned that this statement was not a fair reflection of Servier's involvement with the meeting; some might think that the meeting was organised by The British Journal of Cardiology which was not so. The meeting was infact wholly organised by Servier, the speakers had been briefed by the company and their slides carried prescribing information for Coversyl. Seven staff from Servier attended the meeting but none from The British Journal of Cardiology. The Panel noted that Servier had submitted that the meetings 'would be held under the banner of The British Journal of Cardiology and supported by an educational grant from Servier' and was concerned that this arrangement disguised Servier's true involvement. The Panel requested that Servier be advised of its concerns in this regard.

Complaint received **17 November 2005**

Case completed **16 January 2006**

CASE AUTH/1783/11/05

NOVARTIS v ROCHE

Bondronat journal advertisement

Novartis complained about a Bondronat (ibandronic acid) journal advertisement issued by Roche. Novartis alleged that the claim 'Oral Bondronat is comparable to IV zoledronic acid in bone marker turnover (a measure of bisphosphonate activity)', which was referenced to Body *et al* (2005), was misleading as to the clinical significance of bone marker turnover. By appearing as part of a list of claims in a clinically oriented advertisement, it inferred a clinical comparison using an endpoint that currently did not have a valid role in clinical practice outside of research.

The clinical relevance of bone markers, although being studied, had not been established as a relevant surrogate end point. Novartis alleged that the claim was misleading and did not represent the emerging clinical and scientific information on bone markers and bisphosphonates in a balanced manner.

The Panel noted that the claim 'Oral Bondronat is comparable to IV zoledonic acid in bone marker turnover (a measure of bisphosphonate activity)' followed four other claims all of which related to clinical outcomes or practical advantages for the patient or prescriber. The first three claims related to comparisons of Bondronat with placebo in relation to prevention of SREs, reduction of bone pain and renal safety profile. The fourth point stated that oral Bondronat treatment might be less time and resource consuming than other IV bisphosphonates. The claim at issue referred to a direct comparison between oral Bondronat and IV zoledronic acid and given the context in which it appeared, the Panel considered that some readers would assume that it meant that oral Bondronat had been shown to be clinically comparable to IV zoledronic acid which was not so. There was no data in that regard. Despite the lack of clinical comparison, the Panel noted that Roche had submitted that the claim was intended to be taken into account when making choices regarding treatment options. The Panel considered that the claim was misleading as alleged. A breach of the Code was ruled.

Upon appeal by Roche, the Appeal Board noted that the advertisement featured the question 'Ready to convert?' and considered that in the context of bisphosphonate treatment one of the conversions a clinician might consider would be to change patients from an injectable to an oral agent ie IV zoledronic acid to oral Bondronat. The Appeal Board noted that the claim at issue 'Oral Bondronat is comparable to IV zoledronic acid in bone marker turnover (a measure of bisphosphonate activity)' followed four other claims all of which related to clinical outcomes or practical advantages for the patient or prescriber. The Appeal Board considered that in the context of an advertisement which encouraged doctors to convert patients from one therapy to another, ie make a clinical decision, the claim at issue appeared to supply another piece of clinical information upon which to base that decision and implied that oral Bondronat had been shown to be clinically comparable to IV zoledronic acid which was not so. The Appeal Board considered that the claim was misleading in that regard and upheld the Panel's ruling of a breach of the Code.

Novartis Pharmaceuticals UK Ltd complained about the promotion of Bondronat (ibandronic acid) by Roche Products Limited. The item at issue was an advertisement (ref J116196a) which had appeared in Hospital Doctor, 21 July 2005. Intercompany dialogue had failed to resolve the matter.

Claim 'Oral Bondronat is comparable to IV zoledronic acid in bone marker turnover (a measure of bisphophonate activity)'.

The claim was referenced to Body *et al* (2005).

COMPLAINT

Novartis alleged that the claim was misleading as to the clinical significance of bone marker turnover, in breach of Clause 7.2 of the Code. By appearing as part of a list of claims in a clinically oriented advertisement, it made an inferred clinical comparison using an endpoint that currently did not have a valid role in clinical practice outside of research.

The clinical relevance of bone markers, although being studied, had not been established as a relevant surrogate end point. Some clinical studies had suggested that bone resorption of biomarkers held promise for the assessment of response in metastatic bone disease. However, to date there was little evidence to demonstrate that the reduction of bone-resorption marker levels had a positive effect on common measures of actual clinical outcome such as bone pain and the incidence of skeletal-related events (SREs) (Clamp *et al* 2004). Further trials were ongoing and planned and it was hoped that their results would eventually help to define the use of bone marker directed therapy in clinical practice. However, they had no current role in clinical practice outside of research. This was further substantiated by the American Society of Clinical Oncology (ASCO) 2003 update guidelines in women with breast cancer which stated:

'The use of the biochemical markers to monitor bisphophonate use is not suggested for routine care……the value of bone resorption markers to guide treatment decisions has not yet been shown, for example, to guide initiation of therapy in patients without a prior skeletal event, predict treatment response, guide adjustments to bisphosphonate therapy, or to independently predict future fractures. Each is a worthy goal, but can only be addressed in the research setting.' (Hillner 2003).

Novartis stated that the claim at issue was thus misleading and did not represent the emerging clinical and scientific information on bone markers and bisphosphonates in a balanced manner.

RESPONSE

Roche submitted that the claim was intended to be taken into account when making choices regarding treatment options. Comparative bone marker data was relevant. The data supporting this claim (Body *et al*) was the first head-to-head (Bondronat vs Zometa) study of robust design and statistically sound in patients with advanced breast cancer. Experts in the field of bone marker turnover, and oncologists with no such expertise, had received this study with great interest.

Roche noted that Body *et al* stated 'Bone markers therefore act as useful determinants for assessing clinical responses to bisphosphonate therapy which reduces bone resorption'.

Roche explained that bone markers were collagen breakdown products generated by bone metastases; many clinical publications and clinical experts recognised that these markers were direct measures of bisphosphonate activity in patients. There were many references to support the clinical relevance of bone markers. Some went back to when data was emerging and included the ASCO guidelines 5/2003 cited by Novartis. These guidelines were currently being updated. There were, however, numerous publications that established the clinical relevance of bone markers:

Brown *et al* (2005) stated that 'Biochemical markers of bone metabolism, which reflect both the formation and resorption of bone, can provide valuable insight into tumour and bone interactions and the effects of therapy on this dynamic process'.

Garnero (2001) stated that 'Clearly the established use of bone markers is for monitoring effects of bisphosphonate treatment'.

The role of bone markers was further substantiated by Coleman *et al* (2005). Coleman was an internationally recognised expert in his field. This research was supported by Novartis and the paper looked at the correlation between bone metabolism and clinical outcome during bisphosphonate therapy in three large randomised trials using zoledronic acid (Zometa) in patients with bone metastases. The authors found the correlation between markers and clinical outcomes to be statistically significant and marker assessments at timely intervals during therapy were shown to provide predictive value and meaningful additional data for assessing the risk of negative clinical outcomes in patients with malignant bone disease.

Lipton *et al* (2005a) (sponsored by Novartis) showed that the bone resorption marker N-telopeptide (NTX) provided valuable prognostic information in patients with bone metastases treated with zoledronic acid. At 3 months of treatment, normalisation of elevated baseline urinary NTX was a significant predictor of favourable outcome as measured by SREs and time to first SRE. This was reiterated in another Novartis supported study, (Lipton *et al* 2005b). 'Biochemical markers of bone metabolism provide valuable information about rates of bone turnover in patients with malignant bone disease'. Also, 'Elevated NTX levels [a bone marker] recently have been correlated with increased risks of SREs …'.

Clamp *et al* (2004) discussed the therapeutic response in patients with metastatic bone disease. The paper explained how specific markers of bone turnover could be used to assess therapeutic response in metastatic bone disease and described the BISMARK study as the first study looking at marker directed administration of zoledronic acid.

Pectasides *et al* (2005) showed serum NTX to be a useful marker in monitoring patients with skeletal metastases correlating with the type and bulk of bone disease and reflecting bone disease progression. The authors also commented that it was useful in monitoring bisphosphonate therapy.

Brown *et al* (2003) stated 'a strong correlation between the rate of bone resorption and the frequency of skeletal complications in metastatic bone disease. N-telopeptide also appears to be useful in the prediction of patients most likely to experience skeletal complications and thus benefit from bisphosphonate treatment'.

Lichinitser *et al* (2005) noted 'As markers of bone turnover are prognostic indicators of skeletal complications, the data represented here suggest comparable efficacy for ibandronate and zoledronic acid for preventing skeletal-related events'.

Clemons *et al* (2005) (sponsored by Novartis) discussed 'relevant palliative benefits, reflected by significant improvements in pain scores and bone turnover markers'.

Roche also provided a list of additional references on bone markers and SREs. The company submitted that the clinical relevance of bone markers was well established and being studied further as to how they could be best utilised in the clinical setting.

Roche noted that Novartis had cited the ASCO 2003 guideline that 'The use of biochemical markers to monitor bisphosphonate use is not suggested for routine care'. This was not relevant as the claim 'Oral Bondronat is comparable to IV Zoledronic acid in bone marker turnover (a measure of bisphosphonate activity)' did not suggest bone markers were currently part of routine care. The importance of bone markers lay in the fact that they were an accepted key objective measure of bisphosphonate activity.

Roche noted that the supplementary information to Clause 7.2, emerging clinical or scientific opinion, stated that data must be 'treated in a balanced manner in promotional material'. The claim at issue supported the recognised clinical relevance in terms of the activity of such markers rather than placing emphasis on clinical benefit. ('Activity' was defined in the Concise Oxford Dictionary as, 'vigorous or energetic action', 'natural or normal function', 'as a process'. It did not imply benefit or efficacy).

In summary Roche stated that much time had been taken to carefully word the results of Body *et al* in the advertisement so as not to mislead or claim clinical benefits. In fact, Body *et al* concluded 'As evidenced by reductions in serum markers of bone markers of bone turnover, oral ibandronate suppressed tumor-induced bone resorption as effectively as intravenous zoledronic acid infused every 4 weeks'. Roche noted that it was cautious over the wording of the claim here not to quote 'as effectively' in the claim, where the statistical design was one of non-inferiority.

Roche further noted that Novartis had supported studies and produced data itself that endorsed the clinical relevance of bone markers.

Roche noted the requirements of Clause 7.2 of the Code and submitted that all elements of it were met. The claim was deliberate in content and context. The reference cited and others available supported the claim and the relevance of bone markers. Roche denied a breach of the Code.

PANEL RULING

The Panel noted that the claim 'Oral Bondronat is comparable to IV zoledonic acid in bone marker turnover (a measure of bisphosphonate activity)' followed four other claims all of which related to clinical outcomes or practical advantages for the patient or prescriber. The first three claims related to comparisons of Bondronat with placebo in relation to prevention of SREs, reduction of bone pain and renal safety profile. The fourth point stated that oral Bondronat treatment might be less time and resource consuming than other IV bisphosphonates. The claim at issue referred to a direct comparison between oral Bondronat and IV zoledronic acid. On the basis of the information before it, the Panel did not consider that the claim at issue related to any proven clinical or practical advantage. Body *et al*, cited in substantiation of the claim, had not assessed clinical outcomes of treatment such as incidence of SREs etc. However, given the context in which the claim appeared, the Panel considered that some readers would assume that it meant that oral Bondronat had been shown to be clinically comparable to IV zoledronic acid which was not so. There was no data in that regard. Despite the lack of clinical comparison, the Panel noted that Roche had submitted that the claim was intended to be taken into account when making choices regarding treatment options. The Panel considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

APPEAL BY ROCHE

Roche noted that the Panel had ruled that the claim 'Oral Bondronat is comparable to IV zoledronic acid in bone marker turnover (a measure of bisphosphonate activity)' was misleading in breach of Clause 7.2 of the Code. The Panel had assumed that some readers would consider that the claim inferred oral Bondronat had been shown to be clinically comparable to zoledronic acid. Roche submitted that neither the claim, nor context, set out to mislead.

Roche submitted that certain facts were not in dispute: Body *et al* evaluated patients with advanced breast cancer with bone metastases. This was not an animal model or healthy volunteer trial. The results were statistically significant and valid. Additional and important safety data had been presented from this clinical trial (Body *et al* 2005 (European Cancer Conference (ECCO)), poster). Hence, the results of this trial were not in question.

Roche submitted that this comparative trial showed that one daily tablet of Bondronat was no less effective than a once monthly injection of zoledronic acid in lowering bone markers. The statistical endpoint was to show non-inferiority – in lay terms, both medicines appeared similar.

Roche explained that certain cancers could spread to bone and cause disruption. One of the effects was to release chemicals into the blood called bone markers. This was a well established fact – there was a wealth of published data to support this and, again, this was not in dispute. Bone markers were one of the only truly objective measures of how well a bisphosphonate was acting on the bone.

Roche submitted that the expert reader of this advertisement and those for whom it was intended (and likely to be involved in prescribing bisphosphonates for patients with advance breast cancer) would not be confused or misled as to what were bone markers and the role of bone markers. Bone marker data had featured in all major national and international conferences and was well established in the literature. Indeed, a clarification point was added to the claim to ensure understanding – that bone marker turnover was a measure of bisphosphonate activity. Again, there was a wealth of published literature to support this fact.

Roche submitted that just because a measure was not used widely in the clinic did not mean *per se* it was not of clinical relevance. For example, Positron Emission Tomography (PET) scanners were extremely valuable at imaging the body and were used in research, but few clinicians had access to them. Another example might be in the management of ovarian cancer, where there had been a great deal of use of CA125 serum levels as an indicator of active disease and the need to initiate chemotherapy. However, whilst CA125 was not widely accepted in clinical practice, it was considered clinically relevant and a reliable indicator of disease activity (Niloff *et al* 1986, Rustin *et al* 1989, Bridgewater *et al* 1999).

Roche acknowledged that bone markers were not yet used routinely in the clinic. One reason for this was due to the specialised nature of the assay and laboratory costs. However, a small measuring device was now being developed for routine clinical use. Such a development would make no sense if bone markers were not of clinical relevance.

Roche noted that the BISMARK Study was using bone markers to direct the dose of zoledronic acid given to patients to prevent SREs from bone metastases in advanced breast cancer patients. This would be compared with the standard regular dose of zoledronic acid in a nationwide study of 1,400 patients. The principal investigator in the Study was an internationally acclaimed expert in metastatic bone cancer. BISMARK was supported by the prestigious national cancer trial body CTAAC (Clinical Trials Advisory and Awards Committee) which had approved the scientific and technical merits. BISMARK was opened to recruitment in December 2005 and had full ethics committee approval. This was not a study of the relevance of bone markers. BISMARK accepted the clinical relevance of bone markers and was using them to direct therapy. This trial would be unethical and put half the trial patients at a totally unwarranted risk if bone markers were not considered to be clinically relevant.

Roche noted that the claim appeared at the end of a list of other claims. It did not appear in a different type face or font size. The claim was intended to give the expert reader more information about the two medicines. The results of this trial had been received with great interest by oncologists and had not been challenged as either incorrect or irrelevant.

In summary Roche submitted that this bone marker study generated data that was important for oncologists. Bone markers were clinically relevant. Care was taken to accurately word the claim at issue so as not to mislead or claim clinical benefits. Roche requested the Appeal Board to re-examine this case with the intended audience in mind.

COMMENTS FROM NOVARTIS

Novartis reiterated that current medical opinion still regarded the use of bone markers in the assessment of efficacy of bisphosphonate treatment in skeletal metastases as investigational. As admitted by Roche, the use of bone markers was not routine in current clinical practice.

Novartis stated that this was an area of great scientific interest and a number of research initiatives aimed to further understand their relevance. While these were ongoing, great care must be taken over the interpretation of data from bone markers. There was still no proven quantitative relationship with accepted efficacy measures such as incidence of SREs.

Novartis noted that the BISMARK study aimed to use bone markers to make an estimate of medicine effect in individual patients. The primary endpoint of the study was measured in terms of effect on SREs and not the effect on bone markers. This was because bone markers had not been shown to be an acceptable clinical endpoint. Novartis stated that it would need to wait for the first results of the study in 2008 before further commenting on the use of bone markers as a clinical rather than investigational tool. Novartis enclosed a copy of the study summary.

Novartis noted that Roche had explained that the claim appeared in a list of other claims and was not in a different type face or font, by this it explained that this claim should be given equal emphasis as the other clinical claims. The use of the claim of non-inferiority in effect on bone markers in this context was a clear attempt to claim equivalent clinical efficacy. This was acknowledged by Roche where it re-emphasized its position that bone marker turnover was a measure of bisphosphonate activity. In addition it was also a clear attempt to compare the clinical benefits of the respective medicines as the study was also being used to make additional comparisons regarding the respective safety profiles of Bondronat and zoledronic acid.

Novartis thus alleged that use of the data from Body *et al* to compare the clinical efficacy of two medicines, was misleading in breach of Clause 7.2 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that the advertisement featured the question 'Ready to convert?' and considered that in the context of bisphosphonate treatment one of the conversions a clinician might consider would be to change patients from an injectable to an oral agent ie IV zoledronic acid to oral Bondronat. The Appeal Board noted that the claim at issue 'Oral Bondronat is comparable to IV zoledronic acid in bone marker turnover (a measure of bisphosphonate activity)' followed four other claims all of which related to clinical outcomes or practical advantages for the patient or prescriber. The Appeal Board considered that in the context of an advertisement which encouraged doctors to convert patients from one therapy to another, ie make a clinical decision, the claim at issue appeared to supply another piece of clinical information upon which to base that decision and implied that oral Bondronat had been shown to be clinically comparable to IV zoledronic acid which was not so. The Appeal Board considered that the claim was misleading in that regard and upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal was unsuccessful.

Complaint received	**18 November 2005**
Case completed	**6 April 2006**

GENERAL PRACTITIONER v MENARINI PHARMA

Nebilet patient leaflet

A general practitioner complained about a pad of patient leaflets for Nebilet (nebivolol) she had received from Menarini Pharma. Each leaflet was headed 'Changing your atenolol prescription'. The complainant had thought the leaflets were part of an official directive to change all patients from atenolol to Nebilet but she now understood that they were part of a marketing ploy; she questioned the ethics of this misleading practice.

The Panel noted that the complainant referred to receiving the pad of leaflets from Menarini. The Panel did not know if the complainant had obtained the leaflets via a mailing, direct from a representative or through a third party at the surgery.

The Panel considered that, viewed in isolation, it might be difficult to know where the leaflets had come from or in what context they had been provided. Nonetheless there was no reference on the leaflets to any primary care organisation or other official body; a statement at the bottom of each leaflet made it clear that the leaflets had been provided by Menarini. The Panel did not consider that the leaflets looked as if they were part of an official directive to change all patients from atenolol to Nebilet as alleged. In that regard the leaflets were not misleading. The Panel did not consider that the leaflets were disguised promotion. No breach of the Code was ruled.

A general practitioner complained about a pad of patient leaflets (ref NEB/MJL/304/09.05) for Nebilet (nebivolol) produced by A Menarini Pharma UK SRL. Each leaflet was headed 'Changing your atenolol prescription' and stated:

'A major trial involving a large number of patients in the UK and Scandinavia has recently been completed. One of the conclusions of the trial is that some patients currently being treated with atenolol as part of their medication to control blood pressure could benefit from a change in prescription.

After considering your case, I believe you could benefit from a change in medication from atenolol to Nebilet. Whilst as effective at controlling blood pressure, Nebilet works in a different way to atenolol.'

The leaflet then listed a number of organisations which were sources of information about blood pressure and stated:

'Follow your doctor's advice carefully with regard to dosing and how to take Nebilet. It is possible that your doctor will invite you in for a check-up after changing your medication.'

It was also stated that the leaflet was provided by Menarini as a service to the medical profession and patients.

COMPLAINT

The complainant stated that she had received the pad of leaflets from Menarini and had mistakenly thought that they were part of an official directive to change all patients from atenolol to Nebilet. However, she now understood that it was part of a marketing ploy by Menarini. The complainant questioned the ethics of this type of misleading advertising.

When writing to Menarini, the Authority asked it to respond in relation to the requirements of Clauses 7.2 and 10.1 of the Code.

RESPONSE

Menarini stated that after repeated reading of the leaflet it could not find a reason for the complainant to state that she thought the leaflet '… was an official directive …' to change patients' medicine.

Menarini noted that the complainant stated that she received the pad of leaflets from the company and not from an official NHS or primary care organisation (PCO). The leaflet clearly stated that it was provided '… by: A Menarini Pharma UK SRL' and carried no marking to indicate that it was from an official government body, NHS or PCO. The leaflet carried no instruction to change a patient's medicine.

Menarini noted that the pad of leaflets was either sent to the GP as part of a Nebilet mailing or provided directly by a sales representative. The mailing was sent in a white envelope which had imagery on the cover in colour (no brand name). The letter inside was signed by the Nebilet product manager, had the product name clearly marked and had the company details on the reverse. The four page colour product brochure which was included was clearly marked with the brand and company names and the pad of leaflets clearly stated that it was provided by Menarini.

Menarini explained that the purpose of the leaflet was for a doctor to give to a patient as part of the explanation for their change in medicine after the doctor had considered the case and made the decision that Nebilet was an appropriate part of their patient's treatment. Within the mailing letter there was a sentence that explained how the leaflet might be used by the doctor; 'Also enclosed is a copy of a patient leaflet which you may use to help patients understand the reasons why you have changed their therapy'. As the leaflet was specially intended for use by a doctor with a patient it was deliberately and appropriately low-key and plain in appearance. Menarini considered that if it were anything else it might be accused of advertising to the general public.

Menarini noted that the complaint was dated 24 November 2005; the mailing that included the leaflet was sent to GPs in mid September. The small numbers of leaflets that were held by sales representatives were withdrawn from use between 15 and 22 November.

Menarini denied breaches of Clauses 7.2 and 10.1 of the Code.

PANEL RULING

The Panel noted that the complainant referred to receiving the pad of leaflets from Menarini. The Panel did not know if the complainant had obtained the leaflets via the mailing, direct from a representative or through a third party at the surgery. The complainant had not referred to the mailing.

The Panel considered that, viewed in isolation it might be difficult to know where the leaflets had come from or in what context they had been provided. Nonetheless there was no reference on the leaflets to any primary care organisation or other official body; a statement at the bottom of each leaflet made it clear that the leaflets had been provided by Menarini. The Panel did not consider that the leaflets looked as if they were part of an official directive to change all patients from atenolol to Nebilet as alleged. In that regard the leaflets were not misleading. No breach of Clause 7.2 was ruled. The Panel did not consider that the leaflets were disguised promotion. No breach of Clause 10.1 was ruled.

Complaint received **29 November 2005**

Case completed **10 January 2006**

CASE AUTH/1785/12/05

TEACHING PRIMARY CARE TRUST HEAD OF PRESCRIBING AND PHARMACY v PFIZER

Conduct of representative

The head of prescribing and pharmacy at a teaching primary care trust (PCT) complained that a representative from Pfizer had told potential attendees that a meeting which he, the complainant, had organised, was cancelled, which was not so. The meeting had been arranged to discuss how the PCT could switch large numbers of patients from atorvastatin (Pfizer's product Lipitor) to simvastatin in order to maximise potential cost savings.

The Panel noted that the parties gave differing accounts of events. It was difficult to determine what exactly had transpired. A judgement had to be made on the available evidence.

The Panel noted that the organisation of the meeting in question was nothing to do with Pfizer although its outcome might adversely affect the company's Lipitor sales. From Pfizer's response it appeared that its employees had twice initiated discussions about the meeting. In the Panel's view initiating discussion by asking if the meeting was still going ahead was enough to cast doubt upon it and this was compounded by the mention that not all local general practitioners had been invited. The Panel bore in mind that extreme dissatisfaction was necessary on the part of a complainant before he or she was moved to submit a complaint. The complainant stated that doubts about the meeting going ahead had been put into the minds of two health professionals. The Panel considered that, on balance, the representative had failed to maintain a high standard of ethical conduct and had failed to comply with all relevant requirements of the Code. A breach of the Code was ruled.

The head of prescribing and pharmacy at a teaching primary care trust (PCT), complained about the activities of a representative from Pfizer Limited.

COMPLAINT

The complainant explained that he had arranged a meeting for 24 November for a number of senior consultants from local hospitals, together with general practitioners and pharmacists from local PCTs, to discuss how to switch large numbers of patients from atorvastatin [Pfizer's product Lipitor] to simvastatin in order to maximise potential cost savings arising from the Department of Health's recent price cap on generic simvastatin. The meeting was sponsored by a pharmaceutical company and had taken a considerable amount of effort on the part of PCT and company staff to organise and maximise attendance.

The complainant had found out, via a colleague at another PCT, that a Pfizer representative was telling potential attendees that the meeting had been cancelled. This was untrue, the meeting had not been cancelled. Pfizer representatives were obviously concerned about potential loss of business resulting from a switch to simvastatin.

When writing to Pfizer, the Authority asked it to comment in relation to Clause 15.2 of the Code.

RESPONSE

Pfizer stated that one of its representatives first heard about the meeting from a member of the Professional Executive Committee (PEC) on 1 September. She then informed her colleague – a primary care account manager (PCAM) and the representative in question – of this news.

It was alleged that the PCAM told two health professionals that the meeting had been cancelled. Neither of them had complained about the PCAM's conduct. The first was the prescribing lead for the PCT. Pfizer's PCAM telephoned him around 15 November about another issue. During the course of the conversation he asked him if he was aware of the meeting on 24 November and he seemed to be. According to the PCAM the issue was not discussed further.

The second apparently significant meeting was with the chief pharmacist at a PCT on 18 November. This was a meeting with the PCAM, a local special projects manager and Pfizer's field-based expert on cost:benefit modelling. At the meeting the three Pfizer personnel discussed Lipitor (atorvastatin) data. It was mentioned that local Pfizer sales representatives had noted that some GPs were unaware of the meeting on 24 November. The chief pharmacist stated that she believed that the meeting was still on but would check with the complainant.

The chief pharmacist apparently telephoned the complainant who then complained to the Authority on 21 November. On or around 22 November the PCAM received a telephone message from the chief pharmacist saying that the complainant was unhappy with the situation and was going to ring him. The PCAM telephoned the chief pharmacist reiterating the situation and said he would call the complainant. The complainant called on the same day. The PCAM explained as above and the complainant responded that the meeting was not open to everyone and hence not all GPs would have known about it. The PCAM had had no other contact with the complainant.

Pfizer was confident that its staff had at all times acted in good faith and regretted any misunderstanding that might have prompted the complaint.

Pfizers response was sent to the complainant and his comments invited.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that he became aware of the representative's comments about the meeting in an email from a colleague on 21 November. The colleague had been told by the representative that the meeting was cancelled and that the PCT was having too many problems with the influenza campaign. The complainant noted that this was verified by Pfizer in its meeting notes provided with its response although the report indicated that it was another of Pfizer's employees, not the representative, who mentioned that the PCT 'are snowed under with flu vaccinations'.

The complainant noted that in one of the meeting reports provided by Pfizer, the representative stated 'I can categorically confirm that in no way did I suggest that the meeting […] had been cancelled or postponed', yet the other meeting report stated '[the representative] asked: is the meeting on the 24th Nov still going ahead …' and '[another Pfizer employee] stated […] that [a named doctor] was unsure it would happen'. The complainant noted that he telephoned the representative on 22 November to tell him that he was very unhappy with his behaviour, however the complainant did not entirely agree with Pfizer's version of the conversation – he claimed that there had been a misunderstanding and that he had been told by a doctor that he was unsure as to whether the meeting would go ahead. The doctor in question denied ever having told the representative anything of the sort, and stated that it had been the representative who had raised the issue of the meeting of 24 November stating that he (the representative) understood that it would not be going ahead. The complainant stated that as two of his colleagues had confirmed that it was the representative who had raised doubts about whether the meeting would go ahead, he was sufficiently concerned about the activities of Pfizer's local representatives who were apparently trying to undermine a meeting to which they had not been invited, the outcome of which would significantly reduce prescribing of their biggest selling product, that he formally complained to the Authority. As for Pfizer's comment that neither of his colleagues had made a complaint, the complainant asked, why would they? The meeting was organised by the complainant, not his colleagues and he had told both of them that he would complain to the Authority.

The complainant also asked what business it was of Pfizer to suggest that the volume of work associated with the PCT's influenza campaign would have any effect on a meeting concerning use of statins. All pharmaceutical advisers had wide ranging job descriptions and as senior managers they were required to deal with several issues concurrently.

PANEL RULING

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

The Panel noted that on 15 November the representative had a meeting with a GP to discuss commissioning. At this meeting the representative raised the issue of the meeting on 24 November. At a meeting on 18 November with a chief pharmacist, which the representative attended with two other colleagues, the representative asked if the meeting was still going ahead as it appeared that some GPs did not know about it. One of the representative's colleagues stated that the PCT organising the meeting was extremely busy with the influenza campaign.

The Panel noted that the organisation of the meeting on 24 November was nothing to do with Pfizer although its outcome might adversely affect the company's Lipitor sales. From Pfizer's account of the conversations which had taken place it appeared that Pfizer employees had twice initiated discussions about the meeting. In the Panel's view initiating discussion by asking if the meeting was still going ahead was enough to cast doubt upon it and this was compounded by the mention that not all local GPs had been invited. The Panel bore in mind that extreme dissatisfaction was necessary on the part of a complainant before he or she was moved to submit a complaint. The complainant stated that doubts about the meeting of 24 November going ahead had been put into the minds of two health professionals. The Panel considered that, on balance, the representative had failed to maintain a high standard of ethical conduct and had failed to comply with all relevant requirements of the Code. A breach of Clause 15.2 was ruled.

Complaint received **24 November 2005**

Case completed **8 February 2006**

CASE AUTH/1786/12/05

NHS BOARD PHARMACY AND THERAPEUTICS GROUP v MENARINI PHARMA

Nebilet 'Dear Doctor' letter

An NHS board pharmacy and therapeutics group complained about a Nebilet (nebivolol) 'Dear Doctor' letter sent by Menarini Pharma. The complainant alleged that following a direct quotation from the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) (Dahlof et al), a personal quotation from one of the lead investigators misleadingly implied that ASCOT supported the use of ß-blockers which was not so. The complainant queried whether the lead investigator was happy to have his name attributed to the quotation.

The Panel noted that the 'Dear Doctor' letter discussed the results of ASCOT and included personal comments from one of the lead investigators, who was quoted as stating, *inter alia*, 'Some modern ß-blockers such as nebivolol [Nebilet] have significantly improved cardio-selectivity and lipid profiles, together with a positive effect on vascular endothelium. These 3rd generation ß-blockers may have additional cardiovascular benefits that were not addressed within ASCOT'. The lead investigator was quoted as concluding that '… it is feasible that the 3rd generation ß-blockers may offer advantages over drugs such as atenolol'.

The Panel considered that the key message from the letter was that ASCOT had shown that hypertensive patients currently treated with atenolol would benefit from a change in therapy. It was not sufficiently clear that the implied recommendation that patients should be changed to Nebilet because it had advantages over atenolol was the lead investigator's personal opinion and not that of either Dahlof et al or part of the ASCOT study. The Panel considered that the letter was misleading in that regard and ruled a breach of the Code.

The Panel was satisfied that the quotations attributed to the lead investigator represented his current views. No breach of the Code was ruled in that regard.

The medical director and lead clinician on the pharmacy and therapeutics group of an NHS board complained on its behalf about the promotion of Nebilet (nebivolol) by A Menarini Pharma UK SRL. The material at issue was a 'Dear Doctor' letter (ref NEB/MJL/302/09.05) sent as part of a mailing. The letter was headed 'In the light of ASCOT' (the Anglo Scandinavian Cardiac Outcomes Trial) and discussed the results of the trial and the implications for the treatment of hypertension. The complainant had written to Menarini but was unhappy with its response.

COMPLAINT

The complainant noted that at the bottom of the first page of the letter there was a quotation attributed to one of the ASCOT lead investigators that was favourable for Nebilet. The complainant queried whether the investigator was happy to have his name associated with the quotation.

The penultimate paragraph was a direct quotation from the ASCOT paper (Dahlof *et al* 2005). The final paragraph on that page specifically mentioned Nebilet and the placing of the inverted commas clearly implied that this comment was attributable to Dahlof *et al*.

The complainant noted that Dahlof *et al* stated 'simply indicate particular disadvantages of the specific drugs used – eg atenolol' followed by 'however, pending further information, we believe the combination of ß-blocker and a diuretic should not be recommended in preference to the comparator regime used in [ASCOT] for routine use but only for specific circumstances'. By inserting the final paragraph and indicating or implying that it came from Dahlof *et al* the complainant considered that doctors were being encouraged to prescribe a ß-blocker whereas Dahlof *et al* clearly stated that a ß-blocker and a diuretic should not be recommended.

When writing to Menarini the Authority asked it to respond in relation to Clauses 7.2 and 11.4 of the Code.

RESPONSE

Menarini explained that the 'Dear Doctor' letter was reproduced from a press release that was approved by the lead investigator in question on the day he and his colleagues presented the ASCOT results. The mailing containing the letter was posted within two weeks of that press release. The lead investigator gave his permission for the use of the letter text before the mailing was produced. The letter comments were clearly attributed to the lead investigator and included a properly referenced quotation from Dahlof *et al* of which he was a lead author. Menarini was certain that the letter represented the lead investigator's current views.

Despite the complainant's surprise that the lead investigator had commented favourably on Nebilet, the comments were correctly attributed, referenced and up-to-date, Menarini denied a breach of Clause 11.4 of the Code.

Menarini noted that as the result of another complaint it had already accepted that the letter was misleading and in breach of Clause 7.2 of the Code. The letter had been withdrawn. Menarini noted that it had not intended to mislead and that the text was factually correct.

PANEL RULING

The Panel noted that the 'Dear Doctor' letter discussed the results of ASCOT and at the same time noted some personal comments from one of the lead

investigators who was quoted as stating, *inter alia*, 'Some modern ß-blockers such as nebivolol [Nebilet] have significantly improved cardio-selectivity and lipid profiles, together with a positive effect on vascular endothelium. These 3rd generation ß-blockers may have additional cardiovascular benefits that were not addressed within ASCOT'. The lead investigator was quoted as concluding that 'it is feasible that the 3rd generation ß-blockers may offer advantages over drugs such as atenolol'.

The Panel considered that the key message from the letter was that ASCOT had shown that hypertensive patients currently treated with atenolol would benefit from a change in therapy. It was not sufficiently clear that the implied recommendation that patients should be changed to Nebilet because it had advantages over atenolol was the lead investigator's personal opinion and not that of either Dahlof *et al* or part of the ASCOT study. The Panel considered that the letter was misleading in that regard and ruled a breach of Clause 7.2 of the Code.

The Panel noted Menarini's comments with regard to the generation of the letter and was satisfied that the quotations attributed to the lead investigator represented his current views. No breach of Clause 11.4 was ruled.

Complaint received **9 December 2005**

Case completed **2 February 2006**

CASE AUTH/1787/12/05

BOEHRINGER INGELHEIM/DIRECTOR v SANKYO PHARMA

Breach of undertaking

Boehringer Ingelheim alleged that an Olmetec (olmesartan) journal advertisement, issued by Sankyo Pharma, was in breach of the undertaking given in a previous case, Case AUTH/1681/2/05. Boehringer Ingelheim noted that in the previous case the claim 'There's nothing better to get Margaret to target' was ruled in breach of the Code; the claim now at issue was '...unbeaten at getting Margaret to BP [blood pressure] target'.

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

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

The Panel noted that in Case AUTH/1681/2/05 it had considered, *inter alia*, that the claim 'There's nothing better to get Margaret to target', implied that no other antihypertensive therapy/regimen was better than Olmetec at reducing patients' blood pressure to target. The claim was broad and unequivocal and suggested that every other therapy/regimen had been compared to Olmetec and that none had been shown to be more efficacious. That was not so. The Panel had considered that in that regard the claim was misleading, exaggerated and thus could not be substantiated. Breaches of the Code had been ruled.

Turning to the present case, Case AUTH/1787/12/05, the Panel considered that the claim now at issue, 'Head to head, Olmetec is unbeaten at getting Margaret to BP target' was similar in meaning to the previous one. Smaller text below the claim explained that, in hypertension, head to head studies with Olmetec demonstrated an unbeaten performance vs other classes of antihypertensives. A footnote read 'Compared to captopril, irbesartan, candesartan, losartan, valsartan, amlodipine, felodipine'.

The supplementary information to the Code stated that claims must be capable of standing alone as regards accuracy etc and that in general claims should not be qualified by the use of footnotes. The Panel considered that the claim 'Head to head, Olmetec is unbeaten at getting Margaret to BP target' could not stand alone. In that regard it was closely similar to the one considered previously such that Sankyo had not complied with its undertaking. A breach of the Code was ruled. The Panel considered that by breaching its undertaking, Sankyo had not maintained high standards. A further breach of the Code was ruled. The company had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

Boehringer Ingelheim Limited alleged that a journal advertisement (ref OLM188.1B) for Olmetec (olmesartan medoxomil) issued by Sankyo Pharma UK Ltd was in breach of the undertaking given in Case AUTH/1681/2/05. 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 advice previously given by the Code of Practice Appeal Board.

COMPLAINT

Boehringer Ingelheim stated that the advertisement contained a statement very similar to that found in breach of the Code in Case AUTH/1681/2/05

wherein the claim 'There's nothing better to get Margaret to target' was found to be unacceptable. In the advertisement now at issue the same visual was used, with the claim '… unbeaten at getting Margaret to BP [blood pressure] target'.

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

RESPONSE

Sankyo refuted the allegation that the Olmetec advertisement in question represented a breach of undertaking in relation to Case AUTH/1681/2/05. Furthermore, Sankyo did not consider that it had failed to maintain high standards, nor did it consider the industry had been brought into disrepute as a result. Sankyo therefore denied any breaches of Clauses 2, 9.1 and 22.

In Case AUTH/1681/2/05 Boehringer Ingelheim complained about a number of Olmetec advertisements that featured the claim: 'There's nothing better to get Yvonne bang on' or 'There's nothing better to get Margaret to target'. Boehringer Ingelheim had alleged that both claims were hanging comparisons as the advertisements did not explicitly state what the comparators were. It had also alleged that the claims were misleading and not capable of substantiation. However as stated in the resulting case report 'The Panel did not consider that the claims "There's nothing better to get Yvonne bang on" or "There's nothing better to get Margaret to target" were hanging comparisons as alleged. In the context in which the claims appeared it was clear that the comparison was with all other antihypertensives. The Panel ruled no breach of the Code in that regard'. The Panel went on to state that 'The claims did not exclude the possibility that another antihypertensive therapy/regimen might be equally efficacious'.

The Panel, on the other hand, considered that the advertisements, which featured the aforementioned claims, were misleading and incapable of substantiation because no data was provided within them as to which other antihypertensives were being used as a comparison. The claims therefore could imply that all other antihypertensives, including combination therapy, were being compared and this was not the case. Breaches of the Code were ruled.

Sankyo accepted the decisions of the Panel and provided a signed undertaking and assurance. It subsequently produced a series of revised advertisements, one of which was the subject of this complaint.

Turning to the current case, Case AUTH/1787/12/05, the Olmetec advertisement in question bore the heading: 'Head to head, Olmetec is unbeaten at getting Margaret to BP target'. Sankyo did not consider that this was a hanging comparison for similar reasons described in Case/AUTH/1681/2/05. Just as using the phrase 'There's nothing better' did not imply that Olmetec was the best, the same could be said for the word 'unbeaten'. Instead it only implied that Olmetec was at least as efficacious as its comparators at achieving blood pressure targets and therefore had not yet been beaten in head to head trials.

Although the phrase 'There's nothing better' was not ruled in breach of the Code and therefore not subject to the undertaking provided in Case AUTH/1681/2/05, Sankyo decided to change the claim 'There's nothing better to get Margaret to target' to 'Head to head, Olmetec is unbeaten at getting Margaret to BP target'. The decision to use 'unbeaten' in this instance was purely made on account of needing to produce a revised promotional campaign for Olmetec.

Directly underneath the claim, in prominent text, appeared the following: 'In hypertension, head to head studies with Olmetec demonstrate an unbeaten performance versus other AIIAs [angiotension II antagonists], ACE-Is [angiotension converting enzyme inhibitors] and CCBs [calcium channel blockers] at usual maintenance doses. What's more, 84% of your GMS [general medical services] target is achieved with Olmetec 20mg monotherapy alone by week 8. So choose Olmetec to get more patients like Margaret to BP target'. This information was not provided as a footnote, but instead the text formed an integral part of the advertisement as a whole. Reading both the strapline and the text together the reader was made fully aware of the antihypertensive categories that had been compared in head to head studies as the claim stated ie a number of other AIIAs, ACE-Is and CCBs. It was perfectly reasonable to assume the audience would not interpret this to mean all other AIIAs, ACE-Is and CCBs bearing in mind the large number of available antihypertensives.

The additional information now included on the Olmetec advertisement satisfied, in Sankyo's opinion, the Panel's concern in Case AUTH/1681/2/05 in terms of the claims being too broad and therefore misleading. In addition, Sankyo also included a footnote to specify further details which read 'Compared to captopril, irbesartan, candesartan, losartan, valsartan, amlodipine, felodipine'. The reader could now determine exactly which antihypertensives were used in the head to head comparisons.

The overall impression given by the advertisement in question was significantly different than the one given in Case AUTH/1681/2/05 and Sankyo believed that it was now clear to the intended audience which other antihypertensives were being compared to Olmetec in the head to head studies referred to in the heading.

In summary, Sankyo considered all of the rulings in Case AUTH/1681/2/05 had been addressed and therefore refuted the allegation that the advertisement at issue breached Clause 22. Sankyo considered that high standards had been maintained and that it had not brought the industry into disrepute.

PANEL RULING

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

The Panel noted that in Case AUTH/1681/2/05 it had considered that the claims 'There's nothing better to get Yvonne bang on' and 'There's nothing better to get Margaret to target', implied that no other antihypertensive therapy/regimen was better than Olmetec at reducing patients' blood pressure to target. The Panel considered that the claims were broad and unequivocal and suggested that every other therapy/regimen had been compared to Olmetec and that none had been shown to be more efficacious. That was not so. The Panel considered that in that regard the claims were misleading, exaggerated and thus could not be substantiated. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

Turning to the present case, Case AUTH/1787/12/05, the Panel considered that the bold, headline claim now at issue, 'Head to head, Olmetec is unbeaten at getting Margaret to BP target' was similar in meaning to the previous claim. The Panel noted that text, in a much smaller font size, below the claim stated 'In hypertension, head to head studies with Olmetec demonstrate an unbeaten performance versus other AIIAs, ACE-Is and CCBs at usual maintenance doses'. A footnote to that text, in small type, above the prescribing information at the bottom of the advertisement, read 'Compared to captopril, irbesartan, candesartan, losartan, valsartan, amlodipine, felodipine'.

The supplementary information to Clause 7.2, General, stated 'It should be borne in mind that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like'. The Panel considered that the claim 'Head to head, Olmetec is unbeaten at getting Margaret to BP target' could not stand alone. In that regard the claim was closely similar to the one considered previously such that Sankyo had not complied with the undertaking given in Case AUTH/1681/2/05. A breach of Clause 22 was ruled. The Panel considered that by breaching its undertaking, Sankyo had not maintained high standards in breach of Clause 9.1. The company had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received	**20 December 2005**
Case completed	**16 February 2006**

CASE AUTH/1788/12/05 *NO BREACH OF THE CODE*

CONSULTANT IN RESPIRATORY MEDICINE v ABBOTT

Klaricid leavepiece

A consultant in respiratory medicine complained that a Klaricid (clarithromycin) leavepiece, issued by Abbott, was misleading in its portrayal of the British Thoracic Society's (BTS's) recommendations regarding the treatment of community acquired pneumonia (CAP). The complainant referred to the claim that the BTS recommended Klaricid as a first line treatment for CAP but noted that the BTS guidelines only recommended prescription of a medicine such as clarithromycin (a macrolide) in severe CAP. The complainant considered that 'severe' should be added to the claim.

The Panel noted that the complainant had misquoted the claim at issue. The complainant had stated that it referred to Klaricid whereas it specifically referred to Klaricid IV. The Panel made its ruling based upon what the claim actually stated.

The Panel noted that the BTS guidelines included a table outlining preferred and alternative initial empirical treatment regimens for adults with CAP seen and managed in hospital. Clarithromycin IV was listed as part of a preferred regimen if IV, as opposed to oral, treatment was required for non-severe CAP and also as part of the preferred treatment regimen for all severe CAP. The Panel noted that the BTS guidelines did not recommend administration of an IV macrolide only in severe CAP. The claim 'British Thoracic Society guidelines recommend Klaricid I.V. as a first line treatment for Community Acquired Pneumonia' was thus not misleading or incapable of substantiation on this narrow point and no breach of the Code was ruled.

A consultant in respiratory medicine complained about a Klaricid IV (clarithromycin) leavepiece (ref PXKLA20050307) issued by Abbott Laboratories Limited. The leavepiece detailed the empiric treatment of community acquired pneumonia (CAP) and was distributed exclusively within secondary care.

COMPLAINT

The complainant noted that the leavepiece was entitled 'British Thoracic Society [BTS] guidelines recommend Klaricid [sic] as a first line treatment for Community Acquired Pneumonia' and although this was further and correctly qualified within the leavepiece, it was grossly misleading. The BTS guidelines only recommended prescription of a macrolide in severe CAP, a small percentage of CAPs in total, and indeed the minority even in a hospital setting. The complainant recalled seeing an audit presented at the BTS making just that point; that the commonest mistake in hospital prescription for CAP was overprescription of macrolides. The complainant

considered that the wording should be changed to include the word 'severe' in the heading.

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

RESPONSE

Abbott noted that the complainant quoted as follows from the leavepiece: 'British Thoracic Society guidelines recommend Klaricid as a first line treatment for Community Acquired Pneumonia' whereas the leavepiece referred specifically to the parenteral formulation of Klaricid and stated 'British Thoracic Society guidelines recommend Klaricid **I.V.** as a first line treatment for Community Acquired Pneumonia' (emphasis added).

With regard to the specific concern expressed by the complainant, Abbott stated that the BTS guidelines on the management of CAP recommended the use of macrolides beyond the treatment of severe cases only. As such Abbott did not consider that the leavepiece misinterpreted the latest BTS guidance.

The BTS guidelines summarised the preferred and alternative initial empirical treatment regimens for adults with CAP. Clarithromycin (both the oral and the parenteral formulation) was recommended as a first line treatment for hospital treated CAP, in combination with amoxycillin, ampicillin, benzylpenicillin or a cephalosporin, in all severe cases and those non-severe cases in which patients were previously treated in the community and subsequently hospitalised for clinical reasons.

This leavepiece clearly referred to Klaricid IV on the front page. The BTS guidelines stated that whenever parenteral, empirical antibiotic treatment was recommended, clarithromycin was recommended as part of the 'preferred regimen', justifying its description as 'a first line treatment'. Abbott noted that it did not describe Klaricid IV as the first line treatment.

Abbott submitted that the headline was reinforced by the quotation from the BTS guidelines immediately below, which referred to clarithromycin as 'the preferred macrolide for parenteral therapy …'.

Finally, as the complainant had noted, the leavepiece provided further information on the BTS guidelines and would leave the reader in no doubt as to its precise recommendations laid out within, specifically with regard to the appropriate use of macrolides.

Abbott denied breaches of Clauses 7.2 or 7.4 of the Code.

PANEL RULING

The Panel noted that the complainant had misquoted the claim at issue. The complainant had stated that it referred to Klaricid whereas it specifically referred to Klaricid IV. The Panel made its ruling based upon what the claim actually stated.

The Panel noted that Chapter 8 of the BTS guidelines featured a table outlining preferred and alternative initial empirical treatment regimens for adults with CAP seen and managed in hospital. Clarithromycin IV was listed as part of a preferred regimen if IV, as opposed to oral, treatment was required for non-severe CAP and also as part of the preferred treatment regimen for all severe CAP.

The Panel noted that the BTS guidelines did not recommend administration of an IV macrolide only in severe CAP. The claim 'British Thoracic Society guidelines recommend Klaricid I.V. as a first line treatment for Community Acquired Pneumonia' was thus not misleading or incapable of substantiation on this narrow point and no breach of Clauses 7.2 and 7.4 was ruled.

During its consideration of this case the Panel noted that the BTS guidelines only recommended clarithromycin as part of a first line (preferred) treatment regimen for most hospital treated CAP. This was not made sufficiently clear in the claim at issue. In the Panel's view some hospital health professionals would influence antibiotic policy in the community. Although the leavepiece had only been used in secondary care the Panel considered that it was nonetheless important that the hospital context of the BTS guidance referred to was stated. Neither IV nor oral clarithromycin was a preferred option in the community. Similarly clarithromycin IV was not a preferred option in the hospital treatment of all non-severe CAP; it was only for those non-severe patients who required IV therapy. When non-severe patients had been admitted to hospital for non-clinical reasons or were previously untreated in the community, oral amoxicillin was the preferred option and oral clarithromycin could be used as an alternative. The Panel was concerned that, given the above, the claim at issue was too broad and simplistic to accurately reflect the BTS guidelines. The Panel noted that it had no complaint before it on this point but nonetheless it requested that Abbott be advised of its concerns in this regard.

Complaint received **23 December 2005**

Case completed **14 February 2006**

CASE AUTH/1789/1/06

NHS FOUNDATION TRUST DEPUTY DIRECTOR OF PHARMACY v ASTRAZENECA

Arimidex mailing

The deputy director of pharmacy at an NHS foundation trust complained that an Arimidex (anastrozole) mailing, sent by AstraZeneca, appeared to be non-promotional because the envelope had 'Happy Birthday' printed on the front.

The Panel noted that on the pre-paid envelope at issue 'Happy Birthday' appeared below the recipient's address; a border of 10 stylized candles ran along the bottom edge. The flap on the reverse stated the address to which the envelope should be returned if undelivered. The envelope did not feature a company name nor any other text or design to indicate that the material originated from a pharmaceutical company or was otherwise related to promotion. The Panel considered that the envelope gave the misleading impression that it contained something other than promotional material. The envelope thus constituted disguised promotion of a medicine. A breach of the Code was ruled.

The deputy director of pharmacy at an NHS foundation trust, complained about an Arimidex (anastrozole) mailing (ref AZ 06/05 ARIM 05 16722) sent by AstraZeneca UK Limited. The mailing was sent to mark the fact that Arimidex had been available for 10 years. The envelope had ten stylised candles along its bottom front edge with 'Happy Birthday' written above. The mailing had been sent in November 2005 to all potential Arimidex customers ie breast cancer consultants, specialist registrars, breast cancer nurses, gynaecologists and key pharmacists.

COMPLAINT

The complainant alleged that 'Happy Birthday' on the front of the envelope indicated that this was non-promotional material which was not so. No other wording on the envelope indicated otherwise. The complainant alleged a breach of Clause 10.1, which required that envelopes must not be used for the dispatch of promotional material if they bore words that implied that the contents were non-promotional.

RESPONSE

AstraZeneca submitted that each of the following four points about the envelope in question should have suggested to the recipient that this was not a personal greeting sent by a private individual but was likely to be a promotional offering: the front of the envelope was printed with candles and the words 'Happy Birthday', but it was clear that this printing was an integral part of the envelope; there was a Royal Mail 'postage paid' stamp printed on the front, also as an integral part of the envelope; the name and address of the recipient was attached to the envelope with a pre-printed adhesive label and the reverse of the envelope carried the printed statement 'If undelivered please return to: 42 Somers Road, RUGBY CV22 7XB' in the same colours as the front. Taken together all four points should have conclusively demonstrated to the recipient that this was a commercial mailing and not sent by a private individual.

AstraZeneca apologised unreservedly if this mailing actually arrived on the birthday of the complainant, thereby giving the impression that it might be an unexpected personal greeting. However, the company rejected the assertion that this envelope was in breach of Clause 10.1 as it considered that the nature of the envelope clearly marked it as containing a commercial, promotional mailing.

PANEL RULING

The Panel noted that the mailing had been sent in November 2005. The complaint was thus considered under the provisions of the 2003 Code. The supplementary information to Clause 10.1 stated, *inter alia*, that 'Envelopes must not be used for the dispatch of promotional material if they bear words implying that the contents are non-promotional, for example that the contents provide information relating to safety'.

The Panel noted that the envelope at issue was white with a pre-paid postage stamp in the top right hand corner. The text 'Happy Birthday' appeared below the recipient's address and running along the bottom edge of the envelope was a border of 10 stylized candles. The flap on the reverse of the envelope stated the address to which the envelope should be returned if undelivered. The envelope featured neither a company name nor any other text or design to indicate that the material originated from a pharmaceutical company or was otherwise related to promotion.

The Panel noted AstraZeneca's submission about the design of the envelope but considered that these factors alone were insufficient to negate the misleading impression that the envelope contained something other than promotional material. The envelope thus constituted disguised promotion of a medicine. A breach of Clause 10.1 was ruled.

Complaint received **5 January 2006**

Case completed **3 February 2006**

MEN'S HEALTH PHYSICIAN/GENERAL PRACTITIONER v IPSEN

Conduct of representative

A men's health physician/general practitioner complained that an Ipsen representative had told him that Decapeptyl (triptorelin) could be used in patients with prostate cancer which had spread beyond the gland. The complainant stated that this would therefore include both locally advanced and advanced cancer. Advanced prostate cancer was metastatic; it was considered M1 using standard criteria. Locally advanced cancer was not considered M1 but was present when the cancer had spread beyond the prostatic capsule with or without regional lymph node involvement.

The complainant stated that the representative might have been confused but it was important that representatives and companies quoted specifically the licensed indications for a medicine and did not mislead as to their spectrum of use.

The Panel noted that Decapeptyl was indicated *inter alia* for the treatment of advanced prostate cancer. There appeared to be a difference of opinion as to the definition of advanced prostate cancer. Ipsen submitted that it was any cancer which had spread beyond the prostatic capsule and noted that the Decapeptyl clinical trial data included very few patients with cancer confined to the prostatic capsule; most had disease which extended beyond it but without apparent local nodal involvement or distant metastases. Data in support of the licence application showed that of 485 Decapeptyl patients, 20% were pre-metastatic, 60% were metastatic and the disease status of the rest was unknown. The representatives' briefing material acknowledged that there was some confusion about the term and stated that the licence had been granted on patients with prostate cancer grades C and D meaning that Decapeptyl was licensed for locally advanced and metastatic prostate cancer. The Panel noted the NHS R&D Health Technology Assessment definition which supported Ipsen's submission.

The Panel noted that both the complainant's account of what the representative had said and the representative's briefing material were consistent with Ipsen's definition of advanced prostate cancer ie anything which had gone beyond the prostatic capsule.

On the information before it, the Panel did not consider that the representative had promoted Decapeptyl beyond its licensed indication or had misled the complainant in that regard. However, it was not possible to determine exactly what had happened. Thus no breach of the Code was ruled.

A men's health physician/general practitioner complained about what a representative of Ipsen Ltd had told him about Decapeptyl (triptorelin). Decapeptyl was licensed for, *inter alia*, the treatment of advanced prostate cancer.

COMPLAINT

The complainant alleged that the representative misled as to the licensed indication for Decapeptyl at a recent UK prostate cancer educational meeting supported by medical device and pharmaceutical companies. The complainant believed the meeting was held in early January at the Institute of Physics.

The complainant stated that he met the representative at the Ipsen stand and issues relating to Decapeptyl, which was licensed for advanced prostate cancer were discussed. The representative stated that Decapeptyl could be used in patients with prostate cancer when the cancer had spread beyond the gland. The complainant stated that this would therefore include both locally advanced and advanced cancer. Advanced prostate cancer was metastatic; it was considered M1 using the standard tumour, nodes, metastasis (TNM) criteria. Locally advanced cancer was not considered M1 but was present when the cancer had spread beyond the prostatic capsule with or without regional lymph node involvement.

The complainant stated that there might have been some confusion on the part of the representative but it was important that representatives and their companies quoted specifically the licensed indications for their medicine and did not mislead wittingly or otherwise as to their spectrum of use.

In considering this matter Ipsen was asked to respond in relation to Clauses 3.2, 7.2 and 15.2 of the Code.

RESPONSE

Ipsen stated that the 3rd National Conference on Prostate Cancer: Meeting the Challenge had been held in December 2005 at the Institute of Physics. Two representatives were present at the meeting to staff an Ipsen stand. Ipsen submitted that all information provided to the doctor was consistent with the training the representatives had received on this subject and in line with Decapetyl's licensed indications.

The essence of the case depended on what constituted advanced prostate cancer. The term was not clinically precise and there continued to be genuine debate over exactly what was included in this description. Ipsen sympathised with the complainant as the nomenclature was not used consistently within the medical community. Ipsen stated that advanced prostate cancer was not synonymous with metastatic (M1) cancer, as stated by the complainant.

Prostate cancer – the disease and staging

Ipsen explained that prostate cancer was the most common cancer in men in the UK. The clonal theory of cancer considered the clinical course of prostate carcinoma to begin with a single malignant cell in the prostate gland. Under permissive conditions, this single, aberrant cell grew to form a microscopic focus of cancer within the gland. With time, these cells developed into macroscopic nodules of malignant disease, which were initially confined entirely within

the prostate gland. When large enough, this macroscopic growth could produce the signs and symptoms of prostate enlargement that might lead to its early detection and treatment. Indeed, at this stage whilst the cancer was completely contained within the tough, fibrous prostatic capsule, the treatment target was cure by ablation or extirpation of the tumour. Hormonal manipulation with Decapeptyl was not promoted for this early, localised stage.

However, if the diagnosis at this stage was missed, or treatment was unduly delayed or failed, the continued, unregulated growth of the cancer eventually allowed malignant cells to breach the physical barrier of the prostatic capsule and spread into tissue outside the prostate gland. Initially, these malignant deposits were most likely to be in close proximity to the gland, involving structures such as the seminal vesicle(s), bladder neck and regional lymph nodes. Later, distant metastatic spread via blood and lymphatics carried malignant cells to other locations beyond the pelvis to invade non-regional lymph nodes, bone and soft tissue organs such as the liver, lungs and brain.

Classification of these various steps in the clinical course of prostate cancer were objectively described in the staging of the disease. Two main scales described this staging: the TNM (newer, and more common in Europe) and the Whitmore-Jewett (older, and more common in the USA). Their abbreviated description and equivalence were:

Whitmore-Jewett		**TNM**	
Stage A	Histological (incidental) cancer confined to the prostate	T1	Histological (incidental) cancer confined to the prostate
Stage B	Clinical (palpable or visible) cancer confined to the prostate	T2	Clinical (palpable or visible) cancer confined to the prostate
Stage C	Extracapsular cancer	T3	Tumour extends through the prostatic capsule
C1	No invasion of seminal vesicles	T3a	Extracapsular extension (unilateral/ bilateral)
C2	Invasion of seminal vesicles	T3b	Tumour invaded seminal vesicle(s)
		T4	Tumour fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall
Stage D	Metastatic cancer		
D1	Invasion of pelvic lymph nodes or urethral obstruction causing ureterohydro-nephrosis	N1-3	Involvement of the regional lymph nodes
D2	Bone, visceral or lymph node distant metastases	M1	Invasion to distant metastases
		N0 no regional lymph node involvement	
		M0 no distant metastatic disease	

By combining clinical assessments of the disease stage, histological tumour grade (Gleason score), biochemical markers (prostate-specific antigen levels, serum alkaline phosphatase, prostatic acid phosphatase), life expectancy and the presence of symptoms, internationally recognised treatment algorithms had been developed, and were widely followed. The therapeutic role for hormone manipulation in symptomatic stage C, T3 and T4, and metastatic prostate cancer was firmly established.

However, the description 'advanced' was not used in either scale, and there was no universally agreed point in this clinical spectrum at which local disease, which was confined entirely to the prostate gland, became advanced. Indeed, each step in the staging of this disease could be described as more advanced than that preceding it. By this definition, every stage from stage B or T2 onwards could be considered as advanced. In anatomical terms though, the event that most significantly impacted the prognosis, clinical management and treatment selection in prostate cancer was extension of the tumour through the prostatic capsule. By this practical definition, every stage from stage C or T3 might be thought of as advanced. This approach was supported by the NHS R&D Health Technology Assessment Programme definition which included in the advanced category, prostate cancers which had locally invaded through the prostatic capsule, and/or had involved lymph nodes, and/or had metastases in bone or other organs. However, there was little consensus on the use of this term in scientific publications or in discussion within the medical community.

Clinical trials used for the original licence, Decapeptyl SR 3mg

Ipsen stated that the marketing authorization for Decapeptyl SR 3mg for advanced prostate cancer was granted in 1994. Decapeptyl SR 11.25mg was subsequently granted a licence for the same indication in 2002.

Ten clinical trials were included for assessment in support of the licence application. They included 688 patients and of these, 485 received Decapeptyl SR. At least 95 (20%) had pre-metastatic disease (stage C, M0

or earlier). In 106 Decapeptyl patients the metastatic status was not defined.

When the first Decapeptyl SR marketing authorization for the treatment of prostate cancer was applied for, the term advanced was used and approved in the labelling to conservatively refer to this heterogeneous patient population. Very few patients had locally confined disease (stage A or B; T1 or T2), a significant proportion had disease extending through the prostatic capsule, but without apparent local nodal involvement or distant metastases (stage C; T3, N0, M0 or T4, N0, M0). In recent years, the term locally advanced had been suggested to describe this clinical situation, but this was not commonly used when the UK licence was granted. There remained differences in the use of this new terminology between different research groups and between Europe and the USA. Despite these terminological variations, it was clear that the marketing authorization for Decapeptyl SR was supported and approved on a basis wider than metastatic prostate cancer alone, as feared by the complainant.

Representatives' briefing

Ipsen stated that because of the complexities detailed above and because feedback from prescribers suggested that some clinicians were confused about the interpretation of this approved indication for Decapeptyl SR, a detailed briefing for Ipsen representatives on this subject was prepared last year. A copy was provided.

Stand materials from the meeting

Materials from the stand at the meeting, together with a copy of the graphics used on the stand panels, and the programme from the meeting were provided. This same issue was discussed during much of the second day's agenda. Interestingly, although locally advanced disease (session I) and advanced disease (session II) were handled separately on this day, so too was metastatic prostate cancer (session IV), suggesting that none of these clinical descriptions completely included the others. Furthermore, a review of locally advanced disease was included in the advanced disease session, suggesting the former was a legitimate subset of the latter. In addition, the mechanisms of metastasis were described in the session on locally advanced disease, which by definition should be M0. This illustrated some of the inconsistency in the terminology, even between experts, and might, in part, explain the complainant's concerns if the information provided on classification did not exactly fit with the terminology heard at the meeting.

Conclusions

Ipsen submitted that the Decapeptyl marketing authorization for the treatment of advanced prostate cancer was supported and approved on a wide clinical basis that included many patients with pre-metastatic disease. The licensed description advanced prostate cancer was not used in current staging classifications, and did not have a precise, clinical meaning, other than to exclude early cancers confined to the prostate gland itself. Decapeptyl SR had never been promoted for the treatment of localised prostate disease. Promotion at the meeting was therefore in accordance with its marketing authorization and summary of product characteristics (SPC) (Clause 3.2).

The two representatives who attended the meeting were unable to recall this actual incident. Ipsen was satisfied that their conversation with the complainant on this matter would have been accurate, balanced and fair, and not misleading either directly or by implication (Clause 7.2).

Both representatives would have discharged their responsibilities, to Ipsen specifically and the pharmaceutical industry more generally, ethically and with integrity, in compliance with Clause 15.2 of the Code.

PANEL RULING

This case was considered in relation to the 2003 edition of the Code using the procedure set out in the 2006 Constitution and Procedure.

The Panel noted that Decapeptyl was indicated *inter alia* for the treatment of advanced prostate cancer. There appeared to be a difference of opinion as to the definition of advanced prostate cancer. Ipsen submitted that advanced prostate cancer was any cancer which had spread beyond the prostatic capsule. The company had further stated that the Decapeptyl clinical trial data included very few patients with cancer confined to the prostatic capsule; most had disease which extended beyond the prostatic capsule but without apparent local nodal involvement or distant metastases. An appendix of data showing the patient types included in support of the licence application showed that of 485 Decapeptyl patients, 20% were pre-metastatic, 60% were metastatic and the disease status of the rest was unknown. The representatives' briefing material acknowledged that there was some confusion about the term and stated that the licence had been granted on patients with prostate cancer grades C and D meaning that Decapeptyl was licensed for locally advanced and metastatic prostate cancer. The Panel noted the NHS R&D Health Technology Assessment definition which supported Ipsen's submission.

The Panel noted that the identity of the complainant had not been revealed to Ipsen. The representatives could not remember speaking to the complainant. The Panel noted that both the complainant's account of what the representatives had said and the representative's briefing material were consistent with Ipsen's definition of advanced prostate cancer ie anything which had gone beyond the prostatic capsule.

On the information before it, the Panel did not consider that the representatives had promoted Decapeptyl beyond its licensed indication or had misled the complainant in that regard. However, it was not possible to determine exactly what had happened. Thus no breach of Clauses 3.2 and 7.2 of the Code was ruled. No breach of Clause 15.2 of the Code was also ruled.

Complaint received **2 February 2006**

Case completed **10 March 2006**

CASE AUTH/1795/2/06

GENERAL PRACTITIONER v MERCK SHARP & DOHME

Maxalt email

A general practitioner complained about an email, sent 'In association with MSD', from eMIMS which announced the availability of a new online presentation for doctors containing the latest information about Maxalt (rizatriptan) which was available via a direct link. 'eMIMS MAXALT Presentation: appropriate use in migraine' appeared as a banner across the top of the first page of the email.

The complainant alleged that the email was in breach of the Code because the most prominent display of the name Maxalt, in the banner, was not accompanied by the non-proprietary name.

The Panel noted Merck Sharp & Dohme's submission that transmission of the email was arranged via a third party. The company had approved its input into the email but had not known that introductory text (including the banner) would be added. Merck Sharp & Dohme had not seen the final email. Nonetheless the Panel considered that Merck Sharp Dohme was responsible for the whole of the email which had been arranged on its behalf and would not have been sent without its support. The email promoted Merck Sharp & Dohme's product Maxalt.

The Panel considered that the most prominent display of the brand name was in the banner; the non-proprietary name did not appear immediately adjacent to this display of the brand name. A breach of the Code was ruled.

A general practitioner complained about an email he had received from eMIMS which announced the availability of a new online presentation for doctors containing the latest information about Maxalt (rizatriptan) which was available via a direct link. 'eMIMS MAXALT Presentation: appropriate use in migraine' appeared as a banner across the top of the email. The email had been sent by the editor and director and the editor; below their names appeared the phrase 'In association with MSD', with the company logo. Below this more information was given, including the link to the online presentation and the prescribing information followed by mention of a publications company and instructions for unsubscribing from the mailing list. The email was dated 27 January 2006.

COMPLAINT

The complainant noted that the most prominent display of the name Maxalt occurred at the top of the first page, in the banner, and this was not accompanied by the non-proprietary name. There was a mention of Maxalt to the bottom of the first page which was accompanied by the non-proprietary name. A breach of the Code was alleged.

Merck Sharp & Dohme was asked to respond in relation to Clause 4.3 of the Code.

RESPONSE

Merck Sharp & Dohme stated that the email was sent to health professionals to tell them about an interactive promotional website (edetail) for Maxalt, indicated for the management of the headache phase of migraine attacks. The email was in three parts.

Part 1 was the brief introductory text from the start through to the names of the editor and the director and the MSD logo.

Part 2 was the text that immediately followed the introduction, ie from 'Learn more about Maxalt (rizatriptan) ……..' through to the end of the prescribing information.

Part 3 ran from '© Copyright' through to the end of the email.

Merck Sharp & Dohme explained that it had discussed the edetail project with an agency which had numerous media partners, including a publications company. Through its collaborations with such partners, emails were sent on its behalf to various distribution lists. It was through its partnership with the publications company that the item in question was released.

When the publications company released such communications, (Merck Sharp & Dohme since discovered) a standard section introducing the pharmaceutical company's text was attached so as to reassure the intended audience that the material they were about to read was genuine. In the item in question the section attached was that which was referred to as part 1 above, ie that part of the email containing the specific portion referred to by the complainant.

Thus three parties were involved in the distribution of the email, ie Merck Sharp & Dohme, the agency and the publications company. Merck Sharp & Dohme had a contract with the agency, which in turn had a contract with the publications company. At no time until receipt of the complaint and the subsequent investigation into it was Merck Sharp & Dohme aware of the publications company's intent to insert part 1 and part 3 into the emails sent on Merck Sharp & Dohme's behalf.

As set out above, the text referred to as part 2 above, was the marketing material for the edetail that Merck Sharp & Dohme had developed with the agency and, as such, was the material formally approved by Merck Sharp & Dohme in September 2005. In this approved material, the most prominent mention of Maxalt was at the beginning of the text. Merck Sharp & Dohme was certain that there was no breakdown in its approval process for the material developed with the agency and was comfortable that this material satisfied the requirements of the 2006 Code.

It was clear that, without Merck Sharp & Dohme's knowledge, the agency had instructed the publications company to manage the distribution of

the material on its behalf. By adding its own top section to the approved Merck Sharp & Dohme text, the publications company had created a situation in which the most prominent mention of Maxalt could now arguably be that contained within its own text, previously unseen by Merck Sharp & Dohme. It was through this action that the complaint had arisen. The explanation and culpability had been acknowledged and accepted in full by the agency. Merck Sharp & Dohme respectfully submitted that it was not culpable for the error.

PANEL RULING

This case was considered under the 2006 Code.

The Panel noted Clause 1.2 of the Code which referred to promotion being any activity undertaken by a pharmaceutical company or with its authority which promoted the prescription, supply, sale or administration of its medicines. The Panel noted the submission from Merck Sharp & Dohme that the company was only responsible for part of the email and that it had not known about the publications company's involvement and had not seen the final form of the email. Nonetheless, the Panel considered that Merck Sharp & Dohme was responsible for the whole of the email which had been arranged on its behalf and would not have been sent without its support. The email promoted Merck Sharp & Dohme's product Maxalt.

The Panel considered that the most prominent display of the brand name was in the banner heading to the email. The non-proprietary name did not appear immediately adjacent to the most prominent display of the brand name. Thus the Panel ruled a breach of Clause 4.3 of the Code. (There were no differences between the 2003 Code and the 2006 Code with regard to Clause 4.3.)

Complaint received **6 February 2006**

Case completed **6 March 2006**

CASE AUTH/1796/2/06 *NO BREACH OF THE CODE*

PRIMARY CARE TRUST HEAD OF PRESCRIBING v NOVO NORDISK

Insulin discontinuation announcement

The head of prescribing at a primary care trust complained about a four page leaflet sent by Novo Nordisk entitled 'Discontinuation Announcement'. Page 1 took the form of a 'Dear Colleague' letter and stated that Novo Nordisk's animal insulin range (Pork Actrapid, Pork Mixtard and Pork Insulatard) would not be available after 31 December 2007. The letter referred readers to page 4 of the leaflet, the back page, which featured a chart of alternative preparations (insulin analogues, human insulins and other animal insulins) from Novo Nordisk and other manufacturers. Prescribing information for the Novo Nordisk insulins was included together with a statement as to where it could be found. The date of preparation of the leaflet was January 2006.

The complainant appreciated the company giving the NHS very early notice of this product withdrawal but was concerned that the first sentence of the letter 'As you are probably aware the vast majority of patients with diabetes who require insulin are now initiated on analogue insulins' might not be true; the sentence had little to do with the reason for the letter. It became clearer why the sentence was included when one noted that in the table of possible alternative preparations from Novo Nordisk on the reverse of the letter insulin analogues appeared at the far left while the 'equivalent' human products were in the centre column. In response to a query the complainant had received a similar table of data from the medical information team. This table compared the different products and highlighted the similarities between the human and animal products and also showed the differences compared to the analogue insulin equivalents.

The complainant considered that it was apparent from the inclusion of the first sentence and the layout of the table that the letter was not merely about the discontinuation of animal insulin but also promoted insulin analogues. This was further apparent as the insulin analogues were not available in 10ml vials but in pen style devices (FlexPen and 3ml Penfill) only. Patients changed to this type of insulin would have to change presentation as well as change insulin type.

The complainant was further concerned that the letter was signed by the managing director of the UK and Ireland. This was not someone who should make unreferenced promotional statements to prescribers without any medical evidence for the assertions.

The Panel noted that the 'Dear Colleague' letter on page 1 began with the sentence 'As you are probably aware the vast majority of patients with diabetes who require insulin are now initiated on analogue insulins'. The Panel noted from sales data provided by Novo Nordisk that the market share of analogue insulins was growing and the human and animal insulin market share was decreasing. The animal insulin market, which represented 2% of the total insulin market, was shrinking by 17% a year. The market share at September 2005 was just over 50% for analogue insulins and about 46% for human insulins; animal insulins took the rest. Given the rate of growth of insulin analogues and their market

share, the Panel did not consider it unreasonable to claim that the vast majority of patients were initiated on such products. In that regard the Panel considered that the opening sentence of the letter was not misleading and could be substantiated. No breach of the Code was ruled.

The Panel considered that the leaflet at issue, as well as serving as a discontinuation notice for Novo Nordisk's animal insulins, also informed the reader of the possible alternatives available either from Novo Nordisk or other manufacturers. The leaflet sought to persuade health professionals to switch patients to one of the Novo Nordisk alternatives. Prescribing information for all of the Novo Nordisk products was included. In the Panel's view it was not unreasonable for the managing director to have signed the letter. The Panel considered that the presentation and format of the leaflet was such that its promotional intent was not disguised. No breach of the Code was ruled.

The Panel noted the complainant's comment about unreferenced promotional claims. The Code did not require all claims to be referenced, only those which referred to published studies. Claims had to be capable of substantiation and that substantiation had to be provided to a health professional on request.

The head of prescribing at a primary care trust complained about a four page leaflet (ref INS/525/1205) which he had received from Novo Nordisk Limited, entitled 'Discontinuation Announcement'. Page 1 took the form of a 'Dear Colleague' letter and stated that Novo Nordisk's animal insulin range (Pork Actrapid, Pork Mixtard and Pork Insulatard) would not be available after 31 December 2007. The letter referred readers to page 4 of the leaflet, the back page, which featured a chart of alternative preparations (insulin analogues, human insulins and other animal insulins) from Novo Nordisk and other manufacturers. Prescribing information for all of the Novo Nordisk insulins referred to in the leaflet was on the inside pages, pages 2 and 3, of the leaflet. The letter directed the reader to where the prescribing information could be found and stated that the date of preparation of the piece was January 2006.

COMPLAINT

The complainant stated that whilst he appreciated the company's efforts to keep the NHS informed about its commercial decisions and also the very early notice of this product withdrawal, he was concerned about some of the content of the letter.

The first sentence of the letter stated 'As you are probably aware the vast majority of patients with diabetes who require insulin are now initiated on analogue insulins'. The complainant was unsure if this was true but more importantly this had little to do with the reason for the letter.

It became clearer why the sentence was included when one considered the table of possible alternative preparations from Novo Nordisk on the reverse of the letter. This table placed the insulin analogues at the far left of the table while the 'equivalent' human products were in the centre column. In response to a query the complainant had received a similar table of data from the medical information team. This table compared the different products and highlighted the similarities between the human and animal products and also showed the differences compared to the analogue insulin equivalents.

The complainant considered that it was apparent from the inclusion of the first sentence and the layout of the table on the reverse that the letter was not merely about the discontinuation of animal insulin but also promoted insulin analogues. This was further apparent as the insulin analogues were not available in 10ml vials but in pen style devices (FlexPen and 3ml Penfill) only. Patients changed to this type of insulin would have to change presentation as well as change insulin type.

The complainant was further concerned that the letter was signed by the managing director of the UK and Ireland. This was not someone who should make unreferenced promotional statements to prescribers without any medical evidence for the assertions.

When writing to Novo Nordisk, the Authority asked it to respond in relation to Clauses 7.2, 7.4 and 7.10 of the Code.

RESPONSE

Novo Nordisk submitted that the letter was carefully worded to communicate news that some people found very emotional, ie the discontinuation of medicines. Based on experience, the company knew a good way to formulate such a letter was to explain the reasoning for its decision, break the news and then to offer health professionals support in the process.

Novo Nordisk decided to discontinue its animal insulin range because of their decline in use and the overall popularity of analogue insulins. It was quite relevant to state this fact. Based on IMS British Pharmaceutical Index data, current animal insulin usage represented less than 2% of the total insulin market and was shrinking by 17% per year whereas the total share of all analogue insulins was growing at more than 210% (year on year data) while the human and animal market share was steadily shrinking at just under –100%. Thus, the analogue market share was growing twice as fast as the human and animal insulin shares were shrinking. This demonstrated that the analogue insulins were taking market share from other insulins as patients were migrating from one to the other but more importantly that new insulin patients were mainly started on analogue insulins.

As analogue insulins had the biggest market share and were growing in market share, it thus made sense to put them first in a table of alternatives, before the other less popular options. In this table it was stated that the suggested alternatives did not all come in vials and that patients would need a change device as well, should they choose to use Novo Nordisk's analogue products. Based on market data disposable pens and cartridges for re-usable pen devices were more popular than vials and syringes and thus put the more popular alternative before the least popular

alternative. Novo Nordisk noted that it had listed competitors' animal insulins.

Novo Nordisk took the announcement of discontinuation of products very seriously. This letter, as all important communications, was signed by the most senior person in the company – the Managing Director for UK and Ireland.

All communication regarding the discontinuation process was developed with the full knowledge of the Department of Health as well as Diabetes UK. Both organisations saw the letter before it was sent out.

This letter was the first communication Novo Nordisk had sent to health professionals regarding the discontinuation of animal insulins and no promotional message was intended in stating the reason for this decision. Furthermore, this letter did not mention any specific brands and the company did not believe the letter to be in breach of Clause 10.1 of the Code.

The information provided in the letter was accurate, balanced and fair. There were no claims or comparisons regarding any product that could be seen as promotional. Novo Nordisk denied a breach of Clause 7.2. The market share information of all analogue insulins (from Novo Nordisk and other companies) could be substantiated by IMS data, in compliance with Clause 7.4 of the Code.

PANEL RULING

As the leaflet had been prepared in January 2006, the provisions of Clauses 7.2, 7.4 and 7.10 in the 2006 Code were considered. Clause 7.2 in the 2006 Code was the same as that in the 2003 Code with regard to the need for claims to be accurate and balanced etc. There were no changes to Clauses 7.4 and 7.10 in the 2006 Code.

The Panel noted that the 'Dear Colleague' letter on page 1 of the leaflet at issue began with the sentence 'As you are probably aware the vast majority of patients with diabetes who require insulin are now initiated on analogue insulins'. The Panel noted from sales data provided by Novo Nordisk that the market share of analogue insulins was growing and the human and animal insulin market share was decreasing. The animal insulin market, which represented 2% of the total insulin market, was shrinking by 17% a year. The market share at September 2005 was just over 50% for analogue insulins and about 46% for human insulins; animal insulins took the rest. Given the rate of growth of insulin analogues and their market share, the Panel did not consider it unreasonable to claim that the vast majority of patients were initiated on such products. In that regard the Panel considered that the opening sentence of the letter was not misleading and could be substantiated. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel considered that the leaflet at issue, as well as serving as a discontinuation notice for Novo Nordisk's animal insulins, also informed the reader of the possible alternatives available either from Novo Nordisk or other manufacturers. The leaflet sought to persuade health professionals to switch patients to one of the Novo Nordisk alternatives. Prescribing information for all of the Novo Nordisk products was included. In the Panel's view it was not unreasonable for the managing director to have signed the letter. The Panel considered that the presentation and format of the leaflet was such that its promotional intent was not disguised. No breach of Clause 10.1 was ruled.

The Panel noted the complainant's comment about unreferenced promotional claims. The Code did not require all claims to be referenced, only those which referred to published studies (Clause 7.6). Claims had to be capable of substantiation and that substantiation had to be provided to a health professional on request.

Complaint received **6 February 2006**

Case completed **15 March 2006**

CASE AUTH/1802/2/06

TEACHING PRIMARY CARE TRUST HEAD OF MEDICINES MANAGEMENT v MERCK

Glucophage SR journal advertisement

The head of medicines management at a primary care trust complained about a journal advertisement for Glucophage SR (prolonged release metformin) issued by Merck. The complainant alleged that the claim 'More GI-friendly than IR [immediate release] metformin!' could not be substantiated. No references were cited in support of the claim and the summary of product characteristics (SPC) clearly suggested that gastrointestinal (GI) symptoms were very common with Glucophage SR.

The complainant further stated that the writing in the advertisement was so small he had had to use a magnifying glass to read it.

The Panel noted that the advertisement seemed to have been written across someone's belly. The headline claim 'More GI-friendly than IR metformin!' appeared immediately above a cartoon style smiling face (the mouth of which seemed to be the belly button). The Panel considered that the advertisement implied that GI side effects were not too much of a problem with Glucophage SR. According to the SPC, however, such side-effects occurred very commonly (>1/10) with Glucophage SR as they did with Glucophage (metformin IR). The Panel noted the comparative data submitted but nonetheless considered that the claim, in the context in which it appeared, gave a misleading impression of the absolute incidence of GI effects seen with Glucophage SR which could not be substantiated. Breaches of the Code were ruled.

The Panel noted that the prescribing information at issue was in thin, white type printed on a flesh coloured background. The Panel considered that the poor contrast between the colour of the text and the background was such that the prescribing information was not easy to read. A breach of the Code was ruled.

The head of medicines management at a primary care trust complained about a journal advertisement (ref December 2005. zz27110) for Glucophage SR (prolonged release metformin) issued by Merck Pharmaceuticals which appeared in Prescriber on 19 February.

COMPLAINT

The complainant noted that no references were cited in support of the claim 'More GI-friendly than IR [immediate release] metformin!' except for the reader to obtain further information from the manufacturer. The complainant further noted that the SPC clearly suggested that GI symptoms were very common with Glucophage SR! If the reader wanted to substantiate the claims made by Merck there was nothing to refer to.

The complainant stated that in advertisements with such headline statements, readers should be given a reference to help make the decision for themselves.

The complainant alleged that Merck could not substantiate the claim that Glucophage SR was more 'GI-friendly than IR metformin!' and that it was trying to deceive clinicians.

The complainant further stated that the writing in the advertisement was so small he had had to use a magnifying glass to read it.

When writing to Merck, the Authority asked it to respond in relation to Clauses 4.1, 7.2 and 7.4 of the Code of Practice.

RESPONSE

Merck stated that the Glucophage SR advertisement was developed in a number of sizes such that the smallest version, ie the one at issue, complied with the Code and thus that a lower case 'x' in the prescribing information was at least 1mm in height. Merck's printer had confirmed compliance with regards sizing. Furthermore the prescribing information was clearly positioned alongside the advertisement with short well-spaced lines, emboldened headings and in a contrasting typeface. Merck therefore did not accept there had been a breach of Clause 4.1 of the Code.

Metformin, as an immediate release formulation (Glucophage), had been used for nearly 50 years to treat type 2 diabetes. GI disturbances were widely accepted as the principal adverse effects of treatment and occurred in about 20% of patients. Diarrhoea was the most frequent unwanted effect and although it tended to diminish with time it led to discontinuation of treatment in about 5% of patients (Howlett and Bailey, 1999).

A prolonged-release (SR) form of metformin had been available in the US since October 2000 and was launched in the UK as Glucophage SR in January 2005. In double-blind placebo controlled trials diarrhoea led to discontinuation of Glucophage in 6% of patients. By contrast, as stated in the Physicians' Desk Reference, in placebo-controlled trials with Glucophage SR only 0.6% discontinued due to diarrhoea.

In a double-blind direct comparison of twice daily IR metformin with once daily SR metformin, in those receiving the same total daily dose, the incidence of treatment-emergent GI events was 39% and 29% respectively (Fujioka *et al*, 2003).

A study assessing patients' treatment records from routine clinical care in the US evaluated GI tolerability and incidence of diarrhoea with SR metformin compared with IR metformin. In a group of 205 patients that were switched from IR metformin to SR metformin there was a 50% reduction in the first year of therapy in the frequency of any GI adverse events (26.34% IR, 11.71% SR, $p<0.001$) with a similar

reduction for diarrhoea (18.05% IR, 8.29% SR, p<0.01) (Blonde *et al*, 2004). The switch was also associated with significantly improved GI tolerability in a subgroup of 78 patients that switched from IR metformin to SR metformin with the intention of relieving GI symptoms (p<0.01) (Davidson and Howlett, 2004). When comparing those patients that received metformin for the first time, there was a significantly lower incidence of GI side effects in the first year of treatment on SR metformin (9.23%) than IR metformin (19.83%) (p<0.05). Again the findings were similar for the incidence of diarrhoea (3.08% SR, 13.50% IR, p<0.05) (Blonde *et al*).

The Glucophage SR SPC stated that the nature and severity of adverse events were similar to those reported with immediate release metformin. It was notable that there was no comparative statement with regard to frequency. For frequency of adverse events the SPC only used the crude classification of very common, common etc. Merck acknowledged that the incidence of GI effects with Glucophage SR using this classification was very common ie greater than 1 in 10 patients. However, the evidence cited above demonstrated that although still very common the incidence of GI events with Glucophage SR was lower than that reported with IR metformin.

Therefore the claim that Glucophage SR was 'More GI-friendly than IR metformin!' was accurate, up-to-date, not misleading and capable of substantiation. Merck did not accept there had been a breach of Clauses 7.2 or 7.4 of the Code.

Furthermore, if the complainant had asked Merck for information to support the claim, the references cited above would have readily been supplied in compliance with Clause 7.5 of the Code.

PANEL RULING

The Panel noted that the advertisement seemed to have been written across someone's belly. The headline claim 'More GI-friendly than IR metformin!' appeared immediately above a cartoon style smiling face (the mouth of which seemed to be the belly button). The Panel considered that the advertisement implied that GI side effects were not too much of a problem with Glucophage SR. According to the SPC, however, such side-effects occurred very commonly (>1/10) with Glucophage SR as they did with Glucophage (metformin IR). The Panel noted the comparative data submitted but nonetheless considered that the claim, in the context in which it appeared, gave a misleading impression of the absolute incidence of GI effects seen with Glucophage SR which could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted that Clause 4.1 required prescribing information to be provided in a clear and legible manner. The supplementary information made a number of recommendations to aid legibility; type size was not the only contributory factor. The prescribing information at issue was in thin, white type printed on a flesh coloured background. The Panel considered that the poor contrast between the colour of the text and the background was such that the prescribing information was not easy to read. A breach of Clause 4.1 was ruled.

Complaint received	**23 February 2006**
Case completed	**31 March 2006**

CASE AUTH/1805/3/06

GENERAL PRACTITIONER v LUNDBECK

Cipralex cost comparison bar chart

A general practitioner complained about a cost comparison bar chart for Cipralex (escitalopram) shown to him by a representative from Lundbeck. The bar chart showed the price of Cipralex on the left-hand side and then what appeared to be the price of the generic competitors. One had to look closely to see that the prices shown were in fact those of the branded products of those generic medicines mentioned. The prices of the generic medicines mentioned were on the whole much less expensive than those shown. This gave a totally misleading impression of the cost of Cipralex compared to its competitors.

The Panel noted that the bar chart compared the cost of standard doses of Cipralex with eight products, all mentioned by generic name (*citalopram, duloxetine, *fluoxetine, mirtazapine, *paroxetine, reboxetine, sertraline and venlafaxine XL). The explanation for the asterisk next to citalopram, fluoxetine and paroxetine was given as 'manufacturer's branded price'.

The Panel considered that the basis of the comparison was not sufficiently clear. The cost of all the products was the manufacturer's branded price not just those asterisked. The asterisked products were those where generics were available. The Panel considered that the comparison was misleading and ruled a breach of the Code.

A general practitioner complained about a cost comparison bar chart (ref 0205/ESC/525/176 (1342)) for Cipralex (escitalopram) issued by Lundbeck Ltd.

COMPLAINT

The complainant explained that, *inter alia*, a representative from Lundbeck had shown him a bar chart. This showed at the left-side the price of Cipralex and then what appeared to be the price of the generic competitors. Only on closer inspection was it seen that the prices shown were in fact those of the branded products of those generic medicines mentioned.

The prices of the generic medicines mentioned were on the whole much less expensive than those shown. This gave a totally misleading impression of the cost of Cipralex in relation to its competitors.

When writing to Lundbeck, the Authority asked it to respond in relation to Clause 7.2 of the Code.

RESPONSE

Lundbeck did not consider that the bar chart was misleading under Clause 7.3 of the Code as it compared standard doses of all medicines licensed for treating depression at a cost for 28 days' medication as per MIMS February 2005, therefore like-with-like, and the supplementary information did not preclude – but did not mandate – the use of branded comparators.

It was clear that all the antidepressants in this cost comparison were referred to by their generic names and the branded prices were quoted from the source. Where both generic and branded products existed these were indicated with an asterisk and a footnote which explained that the price stated was that of the branded product.

PANEL RULING

The Panel noted that the bar chart compared the cost of standard doses (28 days) of Cipralex 10mg with eight products, all mentioned by generic name (*citalopram 20mg, duloxetine 60mg, *fluoxetine 20mg, mirtazapine 15mg, *paroxetine 20mg, reboxetine 8mg, sertraline 50mg and venlafaxine XL 75mg). The explanation for the asterisk next to citalopram, fluoxetine and paroxetine was given as 'manufacturer's branded price'.

The Panel considered that the basis of the comparison was not sufficiently clear. The cost of all the products was the manufacturer's branded price not just those with an asterisk beside them. The asterisked products were those where generics were available.

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

Complaint received **1 March 2006**

Case completed **5 April 2006**

CODE OF PRACTICE REVIEW – MAY 2006

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

1726/6/05	**Schering Health Care v Serono**	**Multiple sclerosis project**	**Breach Clause 2 Two breaches Clause 7.2 Breaches Clauses 10.2 and 18.1 Payments to doctors to be recovered Audit required by ABPI Board Public reprimand by ABPI Board Further audit required in June 2006**	**Report from Panel to Appeal Board Report from Appeal Board to ABPI Board**	**Page 3**
1743/7/05 and 1752/8/05	**Anonymous v Boehringer Ingelheim and Pfizer**	**Conduct of representatives**	**Breaches Clauses 2, 9.1, 15.2 and 19.1 Audit of Boehringer Ingelheim required by Appeal Board**	**Appeals by respondents**	**Page 8**
1766/10/05	**General Practitioner v Napp**	**OxyContin mailing**	**Breaches Clauses 7.2 and 7.3**	**Appeal by respondent**	**Page 13**
1767/10/05	**Primary Care Trust Pharmacist v Menarini Pharma**	**Nebilet patient leaflet**	**Breach Clause 20.2 Leaflet and associated mailing to be recovered Audit required by Appeal Board Further audit required in September 2006**	**Report from Panel to Appeal Board**	**Page 16**
1770/10/05 and 1771/10/05	**General Practice Surgery Pharmacist v Sanofi-Aventis and Bristol-Myers Squibb**	**Plavix mailing**	**Two breaches Clause 7.2 Breach Clause 9.1**	**Appeals by complainant and respondents**	**Page 19**
1776/10/05	**Primary Care Trust Pharmaceutical Adviser v Menarini Pharma**	**Promotion of Nebilet**	**Breaches Clauses 7.2 and 20.2**	**No Appeal**	**Page 25**
1779/11/05 and 1780/11/05	**Procter & Gamble and Sanofi-Aventis v Roche and GlaxoSmithKline**	**Bonviva leavepiece**	**Breaches Clauses 7.2 and 7.3**	**Appeal by respondents**	**Page 28**
1781/11/05	Consultant Neurologist v Alliance	Symmetrel leaflet	No breach	No appeal	Page 38
1782/11/05	General Practitioner v Servier	Arrangements for a meeting	No breach	No appeal	Page 41
1783/11/05	**Novartis v Roche**	**Bondronat journal advertisement**	**Breach Clause 7.2**	**Appeal by Respondent**	**Page 46**

1784/11/05	General Practitioner v Menarini Pharma	Nebilet patient leaflet	No breach	No appeal	Page 50
1785/12/05	**Teaching Primary Care Trust Head of Prescribing and Pharmacy v Pfizer**	**Conduct of representative**	**Breach Clause 15.2**	**No appeal**	**Page 51**
1786/12/05	**NHS Board Pharmacy and Therapeutics Group v Menarini Pharma**	**Nebilet 'Dear Doctor' letter**	**Breach Clause 7.2**	**No appeal**	**Page 53**
1787/12/05	**Boehringer Ingelheim/ Director v Sankyo Pharma**	**Breach of undertaking**	**Breaches Clauses 2, 9.1 and 22**	**No appeal**	**Page 54**
1788/12/05	Consultant in Respiratory Medicine v Abbott	Klaricid leavepiece	No breach	No appeal	Page 56
1789/1/06	**NHS Foundation Trust Deputy Director of Pharmacy v AstraZeneca**	**Arimidex mailing**	**Breach Clause 10.1**	**No appeal**	**Page 58**
1794/2/06	Men's Health Physician/ General Practitioner v Ipsen	Conduct of representative	No breach	No appeal	Page 59
1795/2/06	**General Practitioner v Merck Sharp & Dohme**	**Maxalt email**	**Breach Clause 4.3**	**No appeal**	**Page 62**
1796/02/06	Primary Care Trust Head of Prescribing v Novo Nordisk	Insulin discontinuation announcement	No breach	No appeal	Page 63
1802/02/06	**Teaching Primary Care Trust Head of Medicines Management v Merck**	**Glucophage SR journal advertisement**	**Breaches Clauses 4.1, 7.2 and 7.4**	**No appeal**	**Page 66**
1805/03/06	**General Practitioner v Lundbeck**	**Cipralex cost comparison bar chart**	**Breach Clause 7.2**	**No appeal**	**Page 68**

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 prescription only medicines made available to the 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, buy or sell medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the sponsorship of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the 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 William Harbage 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, or the provision of information to the public, 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)
By email to: complaints@pmcpa.org.uk.