NUMBER 66 NOVEMBER 2009

CODE OF PRACTICE REVIEW

PMCPA 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 ABPI Code of Practice for the Pharmaceutical Industry independently of the Association itself.

SELF REGULATION AS THE CORNERSTONE OF THE CONTROL OF MEDICINES ADVERTISING

The PMCPA was pleased to note the continued strong support given to self regulation by the Medicines and Healthcare products Regulatory Agency (MHRA) in the annual report of the MHRA Advertising Standards Unit (http://www.mhra.gov.uk/Howweregulate/Medicines/Advertisingofmedicines/index.htm). The UK model of self regulation supported by statutory regulation as set out in the Memorandum of Understanding between the ABPI, PMCPA and MHRA is of interest worldwide. The PMCPA is often asked to present details of the UK system to trade associations and others outside the UK.

PATIENT CAMPAIGNS AND HEALTH PROFESSIONAL CAMPAIGNS

The view is sometimes expressed that material produced for patients or the public cannot mirror material produced for health professionals. This is not so. Whilst material for patients and the public must, *inter alia*, comply with Clauses 22.1 and 22.2, there is no reason why it cannot have something in common with material for health professionals; for instance the material may have a similar colour scheme. Patients and the public will not see the promotional material for health professionals. If patients show the non-promotional material they have received from a pharmaceutical company to their health professional and the health professional links it to a promotional campaign which they have seen, then so be it.

APPEAL PRESENTATIONS

Companies are reminded that the 'Guidance on Appeal Procedures' states, *inter alia*, that new material, ie material which has not been included in the papers submitted in relation to the case, cannot be introduced at the appeal hearing as set out in Paragraphs 7.4 and 7.5 of the Constitution and Procedure. Presentations at an appeal can only refer to data previously submitted, by either party, in writing to the Authority. It is unacceptable to introduce new material at the appeal hearing itself.

MHRA CONSULTATION

We noted in August that the PMCPA had responded to the MHRA consultation on European Commission proposals on information to patients about prescription only medicines (MLX358). The PMCPA view was that the current UK position should continue. All the submissions, including the PMCPA's together with a summary of the outcome are available on the MHRA website (http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations /MLXs/CON046657).

DIGITAL COMMUNICATION

During the last few months the PMCPA has received some general enquiries about the use of digital communications. We have met a number of interested parties and have also presented at meetings focussing on this area. We are now in the process of producing some questions and answers to give further guidance.

CODE AWARENESS

The PMCPA is working on a pilot project to raise awareness with NHS employees about how to work with the pharmaceutical industry within the requirements of the Code.

CODE OF PRACTICE TRAINING

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

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

The next Code of Practice seminar date on which places remain available is:
Monday, 8 February 2010

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 Nora Alexander for details (020 7747 1443 or email nalexander@pmcpa.org.uk).

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 7747 8880
Facsimile:	020 7747 8881

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7747 8885 or email lmatthews@pmcpa.org.uk).

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

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

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

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

CASE AUTH/2231/5/09

BAYER v BOEHRINGER INGELHEIM

Promotion of Pradaxa

Bayer complained about the promotion of Pradaxa (dabigatran) by Boehringer Ingelheim. The items at issue were a medical information letter and information provided on a Boehringer Ingelheim stand at the British Society for Haematology, April 2009.

Pradaxa was licensed for the primary prevention of venous thromboembolic events in adult patients who had undergone elective total hip or knee replacement surgery. Bayer produced Xarelto (rivaroxaban) which was similarly licensed.

The detailed response from Boehringer Ingelheim is given below.

A letter sent from Boehringer Ingelheim's medical information department to an orthopaedic surgeon noted that the recipient was considering oral antithrombotics in patients undergoing hip or knee replacement surgery and that the letter would update the recipient with information that had become available. Bayer alleged that the letter, which it stated was sent proactively as a mailing rather than in response to an unsolicited request, was promotional and not an objective statement of medical information. High standards had not been maintained.

Bayer noted that the scope of the letter was laid out in the first paragraph as 'the available oral agents for VTE [venous thromboembolism] thromboprophylaxis in patients undergoing hip or knee replacement surgery'. However, under the heading 'Ongoing studies' the letter provided further information about studies in stroke prevention in atrial fibrillation (SPAF) and in VTE treatment. The treatment of SPAF was not connected with VTE prophylaxis in orthopaedic patients.

Bayer alleged that the reference to SPAF and VTE treatment promoted an unlicensed indication and one for which safety was not yet proven in breach of Clause 2.

Bayer alleged that the promotional (and off-label) references to SPAF and other indications constituted a breach of an inter-company undertaking.

Bayer was very concerned about a claim in the letter about the requirement for pre-operation liver function tests (LFTs) relating to alanine transaminase (ALT) for patients on dabigatran: 'This one-off [ALT] measurement … should not typically require the taking of additional blood over and above the usual routine. Importantly, any subsequent LFT testing or LFT monitoring is not required for Pradaxa'. Bayer alleged that the reference to 'usual routine' was misleading because it implied that this blood test was part of the routine pre-operative work-up. However, LFTs were not part of the routine pre-operative work-up as defined by the National Institute for Health and Clinical Excellence (NICE). The claim was misleading and could not be substantiated. Bayer was also concerned that the unqualified claim 'any subsequent LFT testing or LFT monitoring is not required' misled. Changes in liver function parameters were listed as undesirable effects in the Pradaxa SPC, and so Boehringer Ingelheim could not substantiate the claim that measurement of LFTs was not required.

Bayer also alleged that the section entitled 'Balance between efficacy and bleeding' and the statement 'There is some concern as to whether the superior efficacy achieved by Xarelto (rivaroxaban) is at the cost of increased bleeding risk' encapsulated the tone of this entire section of the letter and disparaged rivaroxaban. Bayer alleged that the letter did not represent the balance of evidence with regard to safety results for rivaroxaban.

There was no mention of the positive efficacy benefits and overall positive net clinical benefit demonstrated in each of four rivaroxaban studies (RECORD 1, 2, 3 and 4) and in the pooled analysis of these studies. Bayer's primary efficacy endpoint was reached (and in fact superiority demonstrated) for all individual studies and for the pooled analysis at all time points considered. This fact, and the risk-benefit balance it entailed, was not alluded to in the letter. This omission was disparaging, unbalanced and did not represent the data as a whole. High standards had not been maintained.

Bayer noted that the letter referred to negative information including the Bayer-sponsored RECORD 4 study, but failed to mention the Boehringer Ingelheim equivalent study (REMOBILIZE) which failed to reach its pre-specified primary endpoint. This was a further failure to be balanced and fair.

Bayer alleged that the statement in the letter that the concomitant use of epidural catheters 'needs careful consideration' conflicted with the wording in the summary of product characteristics (SPC) and was likely to confuse.

The Panel noted that both parties agreed that the letter at issue had been sent by Boehringer Ingelheim's medical information department to a health professional. Boehringer Ingelheim

submitted that the letter could take the benefit of the exemption to the definition of promotion set out in the Code; it was a non-promotional response to an unsolicited enquiry from a health professional. The Panel noted that to take the benefit of the exemption the response to an unsolicited enquiry must not be promotional, go beyond the ambit of the original enquiry or be misleading; the response must be accurate. The recipient of the letter at issue wished to remain anonymous and so Boehringer Ingelheim was unable to identify the original enquiry. Boehringer Ingelheim submitted that the request for information would have arisen during the course of a representative visit. Bayer, however, alleged that the letter at issue was sent proactively to the recipient and potentially to many other health professionals. The Panel noted that the burden fell on Bayer to establish its case on the balance of probabilities. Bayer had submitted no evidence to support its submission that the letter at issue was a circular mailing. The Panel considered that the position was complicated in that the identity of the recipient had not been revealed to Boehringer Ingelheim and its author had left the company. The Panel noted that Boehringer Ingelheim acknowledged that it needed to improve the level of detail it recorded for each request; the letter at issue could have been sent to any one of thirteen requests via representatives for information on the comparisons of bleeding and other data between rivaroxaban and dabigatran. In the Panel's view particular care needed to be taken when requests for information resulted from a meeting with a representative. Companies wishing to take the benefit of the exemption to the definition of promotion had to be able to demonstrate that the request was unsolicited.

The Panel noted Boehringer Ingelheim's submission about the scope of the original enquiry. The letter at issue began 'I understand that you are carefully considering the available oral agents for VTE thromboprophylaxis in patients undergoing hip or knee replacement surgery. I wish to take this opportunity to update you with the information that has become available'. The Panel considered that it was not unreasonable to assume that this paragraph reflected the original enquiry.

Pradaxa was licensed for the primary prevention of venous thromboembolic events in adult patients who had undergone elective total hip or total knee replacement surgery. The penultimate paragraph of the letter headed 'Ongoing studies' referred to a study on the use of Pradaxa in SPAF. Pradaxa was not licensed for SPAF. The Panel noted all its comments above about the status of the letter and whether it could take the benefit of the exemption to the definition of promotion. It was unclear whether the enquiry was solicited or unsolicited. The Panel considered that, on the balance of probabilities, by referring to SPAF, the letter might well have gone beyond the scope of the original enquiry outlined at the beginning of the letter which meant that it could not take the benefit of the exemption. The Panel considered that the letter promoted Pradaxa for an unlicensed indication and was inconsistent with the particulars listed in its SPC. A breach of the Code was ruled.

The Panel did not consider that the reference to the unlicensed indication represented a breach of Clause 2.

The Panel noted that the introductory section of the letter referred to the misconception that LFT monitoring was necessary with Pradaxa and stated that the recommendation for Pradaxa was that a one-off baseline ALT measurement be made during the pre-operative assessment. The letter also stated that this one-off measurement to assess the patient should not typically require the taking of additional blood over and above usual routine and that 'Importantly any subsequent LFT testing or LFT monitoring is not required for Pradaxa'. The Panel noted Boehringer Ingelheim's submission that patients routinely gave a blood sample pre-op and that if LFT testing was not normally included it could be added without additional blood being taken. The Panel did not consider that the section at issue misleadingly implied that LFTs were part of the routine pre-operative work defined by NICE as alleged. NICE was not mentioned at all in the letter. No breaches of the Code were ruled. Neither did the Panel consider that the section was misleading as to Pradaxa's safety profile as alleged or incapable of substantiation in this regard. The section discussed the one-off baseline ALT assessment. Adverse events subsequent to administration of Pradaxa was a separate matter. Hepatobiliary disorders occurred in less than 1% of patients. No breaches of the Code were ruled.

The Panel noted that the section entitled 'Balance between efficacy and bleeding' explained that for all new oral anticoagulants there was a need for a balance between efficacy and bleeding risk. It continued 'There is some concern as to whether the superior efficacy achieved by Xarelto (rivaroxaban) was at the cost of increased bleeding risk'. This was followed by a reference to an enclosed summary of the rivaroxaban pooled RECORD study data which included pooled bleed data which showed significance. Bayer stated that it had not been provided with a copy of the summary following a request to Boehringer Ingelheim.

The Panel noted that the review by Frostick discussed the RECORD 1, 2 and 3 studies wherein rivaroxaban was compared with enoxaparin. It was noted that there was no head-to-head comparison of dabigatran and rivaroxaban; Pradaxa and rivaroxaban had each been compared to enoxaparin in separate non-inferiority studies wherein the safety profiles of each showed no statistically significant between group difference. The author concluded that the data seemed to indicate that rivaroxaban might be associated with a greater risk of bleeding which could be a major disadvantage.

The Panel also noted that NICE guidance 170 commented on the RECORD data noting that rivaroxaban at 10mg daily might be more efficacious than enoxaparin in preventing VTE but this was accompanied by a small increased risk of major bleeding. The Committee agreed that on balance rivaroxaban and dabigatran had broadly similar efficacy profiles and noted the need to balance prevention of VTE with possible adverse effects particularly the incidence of major bleeds.

Attached to the letter at issue was, , a pooled analysis of the four RECORD studies based on a presentation by Turpie (2008) and a bleeding definition paper. The RECORD studies each investigated rivaroxaban for the prevention of venous thromboembolism in patients undergoing major orthopaedic surgery vs enoxaparin. The pooled analysis concluded that for the total treatment duration significantly more bleeding was seen with rivaroxaban than enoxaparin for the combined category major bleeding plus clinically relevant non-major bleeding. The published abstract Turpie (2008) concluded, *inter alia*, that rivaroxaban was not associated with a statistically significant increase in the risk of major bleeding. The Panel noted Bayer's submission that only one of the Bayer composite endpoints for bleeding reached significance and only at a single time point that included patients receiving placebo vs rivaroxaban in RECORD 2. Boehringer Ingelheim data on file analysed the bleeding definitions and bleeding rates in the REVOLUTION study programme (Pradaxa) compared to RECORD and noted that a decision was made to change the bleeding definition for the RECORD phase III programme which could be directly responsible for the low overall events rates within the major bleeding category reported in the clinical trials.

The Panel noted that the claim 'There is some concern as to whether the superior efficacy achieved by Xarelto was at the cost of increased bleeding risk' in the letter would be read as a direct comparison with Pradaxa and this was not so. The RECORD studies compared rivaroxaban with enoxaparin. There was only indirect comparative data for Pradaxa and Xarelto. The letter had not provided sufficient detail about the comparisons and was thus disparaging. A breach of the Code was ruled.

The Panel considered that the letter by stating without further explanation that the pooled bleed data 'shows significance' over simplified the position and gave a misleading impression of the totality of the bleed data. A breach of the Code was ruled. On balance, the Panel did not consider that the reference to significance was disparaging as alleged. No breach of the Code was ruled.

The Panel did not consider that the failure to discuss the efficacy of rivaroxaban as demonstrated in the RECORD studies was misleading or disparaging as alleged. The letter made it clear that rivaroxaban achieved superior efficacy. No breaches of the Code were ruled.

The Panel noted Boehringer Ingelheim's submission that medical information was rarely asked about the relative efficacy of rivaroxaban and Pradaxa. The letter referred to the balance between efficacy and bleeding it did not detail the products' relative efficacy and thus the Panel did not consider that the failure to refer to the REMOBILIZE study was misleading as alleged. No breach of the Code was ruled.

The Panel noted that the letter stated that the insertion/removal of epidural catheters in the presence of an anticoagulant needed careful consideration and referred to an enclosed information sheet. The Panel noted the Pradaxa SPC stated that Pradaxa was not recommended for use in patients undergoing anaesthesia with post-operative indwelling epidural catheters. The Panel noted that whilst this cautionary wording was reflected in the information which accompanied the letter, the letter had to be able to stand alone as regards the requirements of the Code. The Panel considered that given the wording of the SPC the letter was misleading about the concomitant use of catheters and the administration of Pradaxa and inconsistent with the particulars listed in its SPC. Breaches of the Code were ruled.

The Panel noted that its rulings of breaches of the Code outlined above demonstrated that the letter was, in part, inaccurate and misleading were further reasons why the letter could not take the benefit of the exemption to the definition of promotion.

The Panel noted that Bayer had also alleged a breach of the Code as the letter was promotional throughout and not an objective statement of medical information. The Panel considered that health professionals and others should be able to rely upon medical information departments as a source of objective information about products. The Panel noted its rulings of breaches of the Code and the Panel considered that the letter as a whole failed to maintain high standards. A breach of the Code was ruled.

Bayer alleged that Boehringer Ingelheim's stand at a meeting of the British Society for Haematology, April 2009 promoted ongoing clinical trials of dabigatran in unlicensed indications, including life size trial logos in brand colours. Bayer alleged a breach of the Code because it was not in accordance with the terms of the Pradaxa marketing authorization. The safety and efficacy data for these trials were not yet available.

Bayer alleged that this provision of information about clinical trials was promotional in nature in breach of the Code including Clause 2.

The Panel noted that the exhibition stand presented information about the REVOLUTION clinical trial programme: acute VTE treatment;

secondary VTE prevention; SPAF and secondary prevention of cardiac events in patients with acute coronary syndrome. The Panel noted the submission that the stand had been set up to meet an anticipated demand for information beyond VTE prevention. The Panel disagreed with the submission that only interested physicians would visit and seek information. The stand panels included a section listing features of dabigatran, a reference to what appeared to be a Boehringer Ingelheim meeting 'A Question of Anticoagulation' and stated that medical information was available on request. In the Panel's view such a statement would solicit requests. Boehringer Ingelheim submitted that the logos used on the stand were for the clinical studies mentioned and no product branding was included. The stand was manned by medical affairs and medical information staff. Boehringer Ingelheim had provided the briefing document to the sales team regarding UK congresses which stated that the REVOLUTION stand was used in addition to the normal branded stand pre-launch.

The Panel was concerned about the stand; its presence demonstrated a poor understanding of the requirements of the Code. Placing documents on an exhibition stand amounted to an invitation to take them. The Panel considered that the exhibition stand at issue solicited enquiries about dabigatran and the REVOLUTION clinical trial programme. The Panel noted that Pradaxa was licensed for the primary prevention of VTE following elective total hip or total knee replacement surgery. The Panel considered that the exhibition stand promoted Pradaxa for unlicensed indications and this was inconsistent with the SPC. A breach of the Code was ruled. As Pradaxa was promoted prescribing information needed to be provided or made available at the stand. A breach of the Code was ruled. The Panel did not consider that the promotional activity was disguised as alleged. No breach of the Code was ruled. The Panel did not consider that the stand at issue represented a failure to disclose details of clinical trials as required by the Code. The supplementary information to that clause reminded companies that such information must not constitute promotion. That aspect was covered by the Panel's rulings outlined above. No breach of the Code was ruled.

Although seriously concerned about the stand, on balance the Panel did not consider that a ruling of a breach of Clause 2 of the Code was warranted. This was reserved for use as a sign of particular censure.

Bayer plc complained about the promotion of Pradaxa (dabigatran) by Boehringer Ingelheim Limited. The items at issue were a medical information letter and information provided at a Boehringer Ingelheim stand at the British Society for Haematology, 49th Annual Scientific Meeting, 27-29 April 2009.

Pradaxa was licensed for the primary prevention of venous thromboembolic events in adult patients who had undergone elective total hip replacement surgery or total knee replacement surgery. Bayer produced Xarelto (rivaroxaban) which was similarly licensed.

* * * * *

The Panel noted that although Bayer had not always cited specific sub-clauses of the Code when alleging breaches of Clauses 3, 7, 8 and 9, it had provided sufficient information such that its allegations clearly related to specific sub-clauses. Nonetheless the Panel noted that complainant companies should always cite the specific sub-clauses to be considered.

1 Medical information letter

A letter sent from the medical information department, Boehringer Ingelheim, to a health professional noted that the recipient was considering oral antithrombotics in patients undergoing hip or knee replacement surgery and that the letter would update the recipient with information that had become available. The health professional to whom the letter was addressed had proactively given an anonymised copy of it to Bayer.

COMPLAINT

Bayer alleged that this letter was sent proactively to an orthopaedic surgeon (and hence potentially to many other health professionals as a circular mailing) rather than in response to a genuine unsolicited request. This was a breach of Clause 1.2 firstly because the first paragraph stated 'I wish to take this opportunity to update you …' and 'information that has become available' rather than 'Further to your request for information …' which would normally be the correct procedure for an unsolicited request for information. Secondly, the recipient felt that anonymity would be ensured by removing his name and the date from the top of the letter; he did not view this as an individual personalised letter sent specifically to him, but rather as a widely circulated piece.

Bayer alleged that the letter was promotional in tone throughout, and was not an objective statement of medical information. As well as the breach of Clause 1, this constituted a failure to maintain high standards in breach of Clause 9. Use of the brand name, Pradaxa rather than the generic name dabigatran, which was customary in non-promotional communications, particularly in relation to prescribing indications in respect of which no marketing authorization had been granted. Further, promotional statements and disparaging comments were made about competitor products – especially rivaroxaban – throughout the letter.

Bayer alleged that the scope of the letter was wider than would be the case for a response directly and solely related to the particular enquiry as stipulated

in Clause 1.2. The scope of the letter (whether genuinely unsolicited or otherwise) was laid out in the first paragraph as 'the available oral agents for VTE [venous thromboembolism] thromboprophylaxis in patients undergoing hip or knee replacement surgery'. In contrast to this, under the heading 'Ongoing studies' the letter provided further information about Boehringer Ingelheim studies in stroke prevention in atrial fibrillation (SPAF) and in VTE treatment. The treatment of SPAF was not connected with VTE prophylaxis in orthopaedic patients.

Bayer alleged that the inclusion of SPAF and VTE treatment constituted a breach of Clause 3; the comparative statement about dabigatran's SPAF timelines as being 'ahead in terms of timescale ... of all new anticoagulants' gave the letter an overtly promotional tone. Boehringer Ingelheim did not have a marketing authorization for dabigatran in these indications, and in addition, the safety and efficacy results of these studies were not yet known. Bayer alleged that the letter therefore promoted an unlicensed indication and one for which safety was not yet proven in breach of Clause 2. Use of the brand name Pradaxa rather than dabigatran introduced a promotional tone.

Bayer alleged that following Boehringer Ingelheim's satellite symposium at the meeting in 2008 and subsequent inter-company dialogue, Boehringer Ingelheim gave an assurance that it would be more sensitive about the perception of off-label promotion of dabigatran in SPAF in future. However the promotional (and off-label) references to SPAF and other indications constituted a breach of the undertaking given by Boehringer Ingelheim, in breach of Clause 25, and reopened the issue of the satellite symposium invitation according to the inter-company agreement.

Bayer was very concerned about the following sentences in the medical information letter relating to the requirement for pre-operation liver function tests (LFTs) relating to alanine transaminase (ALT) for patients on dabigatran: 'This one-off [ALT] measurement … should not typically require the taking of additional blood over and above the usual routine. Importantly, any subsequent LFT testing or LFT monitoring is not required for Pradaxa'. Bayer alleged that the section about 'usual routine' was misleading because it implied that this blood test was part of the routine pre-operative work-up. However, LFTs were not part of the routine pre-operative work-up as defined by the National Institute for health and Clinical Excellence (NICE). The claim was misleading and could not be substantiated in breach of Clause 7.

Bayer was particularly concerned that the unqualified claim 'any subsequent LFT testing or LFT monitoring is not required' was misleading as to the safety profile of dabigatran. Derangements of liver function parameters were listed as undesirable effects in the Pradaxa SPC, and therefore Boehringer Ingelheim could not substantiate the claim that measurement of LFTs was not required in breach of Clause 7.

Bayer also alleged that in the section entitled 'Balance between efficacy and bleeding', the statement 'There is some concern as to whether the superior efficacy achieved by Xarelto (rivaroxaban) is at the cost of increased bleeding risk' encapsulated the tone of this entire section of the letter and disparaged rivaroxaban, in breach of Clause 8.

Bayer alleged that the letter did not represent the RECORD safety results for rivaroxaban as a whole – only of the single significant adverse safety composite result. Bayer noted that only one of the composite endpoints for bleeding reached significance, and only at a single time point that included patients receiving placebo vs rivaroxaban in RECORD 2. None of the other composite or single safety endpoints reached statistical significance at any time point considered. Despite this, however, the wording in the medical information letter 'this includes pooled data (which shows significance) …' implied that overall the pooled data demonstrated a significant increase in bleeding rates. This was disparaging and unbalanced in breach of Clauses 1, 7 and 8.

There was no mention of the positive efficacy benefits and overall positive net clinical benefit demonstrated in each of the rivaroxaban studies (RECORD 1, 2, 3 and 4) and in the pooled analysis of these studies. Bayer's primary efficacy endpoint was reached (and in fact superiority demonstrated) for all individual studies and for the pooled analysis at all time points considered. This fact, and the risk-benefit balance it entailed, was not alluded to in the letter. This was disparaging in breach of Clause 8, unbalanced and did not represent the data as a whole (Clause 7). This was inappropriate wording for a medical information letter which would be expected to be objective (Clause 1). This was a clear failure to maintain high standards (Clause 9).

Bayer noted that the letter referred to negative information including the Bayer-sponsored RECORD 4 study, but failed to mention the Boehringer Ingelheim equivalent study (REMOBILIZE) which failed to reach its pre-specified primary endpoint. This was a further failure to be balanced and fair as required by Clauses 1 and 7.

The letter referred to an 'enclosed information sheet'. In view of its concerns expressed above Bayer asked for a copy of this information sheet as it suspected that it might contain similarly biased reporting. However this request was not acceded to by Boehringer Ingelheim.

The letter failed to make it explicit that the concomitant use of epidural catheters was 'not recommended' in the Pradaxa SPC. On the contrary, the statement in the letter that this 'needs careful consideration' conflicted with the wording in the SPC and was likely to confuse. The reference to

'careful consideration' was outside Pradaxa's label (breach of Clause 3). Bayer alleged that referring the reader to a separate enclosure without describing the content of the enclosure in the main text was inadequate to get around this, in the same way that Clause 7 stated that claims should not be qualified by the use of 'footnotes and the like'. The use of the separate enclosure was a breach of Clause 7.

In inter-company dialogue, Boehringer Ingelheim stated that it was difficult to investigate Bayer's complaint without knowing who the customer was. Boehringer Ingelheim did not refer to any discussion of the matter with the medical information officer who wrote the letter or to any search of the medical information database to find the original specific enquiry.

RESPONSE

Boehringer Ingelheim explained that medical information sent the letter in response to an unsolicited request for information from a health professional. The request would have been forwarded to medical information by a sales representative using the company's information system. As was normal practice the response consisted of specific pre-prepared sections and/or attachments that covered the matters of the request. Subsequent investigation of the details of the requesting physician, the specific sales representative and the details of the request had been hampered by the fact that the medical information officer in question had left Boehringer Ingelheim.

Boehringer Ingelheim submitted that although the date was obscured the letter was sent in 2009. The company's information system showed that between 1 January 2009 and 18 February 2009 the medical information department sent out thirteen responses with information on the comparison of bleeding and other data between rivaroxaban and dabigatran.

Boehringer Ingelheim submitted that this was the first time that it had needed to analyse the system to identify a specific request in this way and by undertaking this process it recognised a need for further improvement in the level of detail recorded for each request. This was being implemented for future requests. Boehringer Ingelheim had re-enforced to the field force to clearly outline how and what to request through medical information. Boehringer Ingelheim had also re-emphasised to its medical information team the importance of the most optimal response to customer enquiries. Boehringer Ingelheim informed Bayer of this (7 May 2009).

Unfortunately, without further information, Boehringer Ingelheim had not been able to identify the specific request that this letter related to.

Boehringer Ingelheim submitted that the request for comparative information on rivaroxaban and dabigatran in this letter would have arisen during the course of a representative visit to a health professional. This was, not surprisingly, a common request as there were just two relatively new oral anticoagulants for VTE prophylaxis associated with knee and hip replacement surgery and decisions on which to include in potential formularies or to prescribe were influenced by differences in recommendations or performance in specific clinical situations. Boehringer Ingelheim submitted that some clinicians considered that a formulary application was unlikely to be successful for VTE prophylaxis in isolation and so they requested further information on the likely timings of a wider range of indications. This was why information on ongoing off-label studies was included. The representative forwarded such requests to medical information and the response was sent directly to the health professional.

Boehringer Ingelheim denied that this letter was sent proactively to a number of health professionals. For the reasons outlined above, the recipient could not be identified but as a policy medical information responses were specific and sent only upon receipt of a request.

Boehringer Ingelheim disagreed that medical information letters must begin with 'Further to your request for information …' or the like. Indeed in this case the breadth of requested information would make such an introduction quite cumbersome as it would require all the topics covered to be listed. However, to avoid the possible motive for a future medical information letter being similarly misunderstood, Boehringer Ingelheim had instructed the medical information team to refer, within the introductory paragraph, to the sales representative visit from which the request had arisen and to ensure there was a clear reference to specific requests for each of the subjects covered in the response.

Boehringer Ingelheim denied that the letter was promotional in tone throughout and was not objective. 'Pradaxa', which appeared more than once in the body of the letter and also in the information sheet related to epidural anaesthesia, was not used throughout; dabigatran was used on a number of occasions. Including the brand name more than once in the letter was an oversight which had been corrected as referred to in inter-company dialogue. However, while minimising use of the brand name was good practice, Boehringer Ingelheim did not consider its use was necessarily a breach of the Code. The format of the communication was clearly a letter and it did not appear promotional.

Boehringer Ingelheim disagreed with Bayer's submission that the scope of the letter was wider than would be the case for a response directly and solely to a particular enquiry. In considering points of difference between dabigatran and rivaroxaban, the topics included in this letter were all relevant and ones upon which Boehringer Ingelheim was

frequently asked for information either individually or in combination. As described above, the progress of ongoing studies in indications which health professionals seemed to perceive as more important than VTE prophylaxis in knee and hip replacement surgery was an area of considerable interest and therefore a frequent subject of request. Boehringer Ingelheim was unable to comment upon whether the recipient of this letter was an orthopaedic consultant. The information presented on ongoing studies was factually correct and the content was entirely appropriate in a medical information response to an unsolicited request for information. Boehringer Ingelheim denied that this was promotional and did not agree that this was in breach of Clause 3 of the Code as alleged. Further, in relation to the provision of information on ongoing studies Bayer alleged a breach of undertaking with regard to previous inter-company dialogue in a separate matter. Boehringer Ingelheim understood however that Clause 25 related to undertakings in respect of rulings under the Code which would not apply in this case.

Boehringer Ingelheim disagreed with Bayer's allegation that the information about the requirement for LFTs with dabigatran was misleading. The statement 'This one off [ALT] measurement …should not typically require the taking of additional blood over and above the usual routine. Importantly subsequent LFT testing or LFT monitoring is not required for Pradaxa' was accurate and reflected both the Pradaxa SPC and clinical practice. The section about usual routine was accurate and was not misleading as routine pre-operative work-up normally included venepuncture for blood chemistry (and haematology). Where LFT was not normally included in the routine blood chemistry analysis it could be added (usually by box ticking on the same request form) and no additional blood would be required for this analysis. It was also possible that where routine pre-operative screening without LFT had been completed the laboratory might be asked over the following few days to perform LFTs on the retained sample. That NICE did not include LFT in routine pre-operative work-up was irrelevant as Boehringer Ingelheim did not indicate that this was routine. Boehringer Ingelheim indicated only that LFT could be undertaken without need for additional blood. The further statement that any subsequent LFT testing or monitoring was not required was accurate and consistent with the SPC. It was correct that derangements of LFTs were included among the adverse reactions reported with dabigatran but this was an entirely separate matter from any requirement for routine monitoring of LFT subsequent to the pre-operative sample. Request for clarification of the requirements for LFT testing with dabigatran was not infrequent from health professionals who had received misinformation on the requirements for LFT monitoring with dabigatran.

Bayer had complained that the statement 'There is some concern as to whether the increased efficacy achieved by Xarelto is at the cost of increased bleeding' disparaged rivaroxaban. Boehringer Ingelheim submitted that this was an accurate statement that reflected both clinician views (Frostick 2009);

> 'The safety data, however, seem to indicate that rivaroxaban may be associated with a greater risk of bleeding (as shown in the pooled data analysis). As surgical site bleeding is the major concern for orthopaedic surgeons, increased bleeding risk with rivaroxaban could be a major disadvantage for the drug', and

The NICE technology appraisal guidance 170:

> '4.5 The Committee discussed the results of the RECORD studies and concluded that rivaroxaban was at least as effective as enoxaparin in preventing VTE. The Committee considered adverse events such as bleeding, noting that the relative risk of major bleeding numerically favoured enoxaparin. The Committee noted that the chosen dose of rivaroxaban appeared to increase efficacy in prevention of VTE after surgery, with a small increase in risk of major bleeding when compared with enoxaparin. It concluded that rivaroxaban at its licensed dosage of 10 mg daily might be more efficacious than enoxaparin in preventing VTE but this was accompanied by a small increased risk of major bleeding. The Committee was persuaded by testimony from the clinical specialists that there was a 'brand off' to be made between increasing anticoagulant efficacy and the risk of adverse effects, including major bleeding.
>
> 4.6 The Committee considered evidence on the clinical effectiveness of rivaroxaban compared indirectly with dabigatran that showed that rivaroxaban significantly reduced the relative risk of the major primary endpoints. However, the Committee noted that in this analysis the relative risk of major bleeding favoured dabigatran although this difference was not statistically significant. It agreed that on balance, rivaroxaban and dabigatran had broadly similar efficacy profiles, and noted the need to balance prevention of VTE with possible adverse effects, particularly the incidence of major bleeding events.'

In addition to this, the FDA Advisory Committee Briefing Document for New Drug Applications 22-406 addressed the concerns of bleeding events for patients undergoing total hip or knee replacement surgery receiving treatment of rivaroxaban compared with enoxaparin.

Bayer had expressed a number of concerns related to the two paragraphs headed 'Balance between efficacy and bleeding'. It was well established that

with anticoagulants increased effect was associated with an increased risk of bleeding although clearly this needed to be demonstrated for individual products.

It was important to understand the context of the requests for information and therefore also the responses. Rivaroxaban had demonstrated superior efficacy to enoxaparin in an extensive phase III clinical trial programme whereas dabigatran had shown non-inferiority to enoxaparin (in a phase III programme designed with this objective). The efficacy of rivaroxaban was generally well accepted by clinicians (and Boehringer Ingelheim) and medical information was rarely asked about relative efficacy.

Understanding of the risks of bleeds with rivaroxaban relative to dabigatran was very difficult to assess objectively based upon the clinical study data. In the rivaroxaban clinical studies the definitions of bleeding events were different from the traditional definitions used in the studies of dabigatran and other products in this area. Related to this the rate of bleeding events for both active and control were much lower in the rivaroxaban studies than in studies of dabigatran and other earlier products eg enoxaparin and fondaparinux. Understanding differences in the definitions of bleeding events between studies was clearly critical to interpretation of results. Many clinicians did not know of these differences but when they did they requested specific information.

Boehringer Ingelheim submitted that this letter provided such information. Copies of the rivaroxaban and dabigatran publications and published information from the pooled analysis conducted by Bayer were provided.

Boehringer Ingelheim submitted that in the individual rivaroxaban studies there were no significant differences in bleeding events between rivaroxaban and enoxaparin although numerically the incidence of bleeding was greater with rivaroxaban. The low overall incidence of major bleeding events, at least in part related to the restrictive definition of an event, would statistically reduce the likelihood that a numerical difference would achieve statistical significance. Bayer undertook a pooled analysis of efficacy and safety endpoints and it was these data that Boehringer Ingelheim had summarised in its response.

Boehringer Ingelheim submitted that the statements in the letter in conjunction with the information sheets, which provided the details reflected an accurate and balanced review relevant to a request for clarification of differences in bleeding definitions used in the dabigatran and rivaroxaban study programmes and an objective view of the bleeding risk with rivaroxaban (relative to enoxaparin).

Boehringer Ingelheim submitted that with regard to the information on 'concomitant use of epidural catheters' it was important to consider the context within which the information was provided, specifically a request for comparative information on rivaroxaban and dabigatran and their use with epidural catheters. Boehringer Ingelheim submitted that the paragraph in the body of the letter was clear and accurate and specifically referred the reader to the enclosed information sheet. It made only a general statement without any specific statement about the use of either product in relation to epidural catheters. Boehringer Ingelheim submitted this was clear, unambiguous and would not confuse. The information sheet enclosed with the letter provided the detailed information and was similarly accurate, unambiguous and reflected the SPCs.

Copies of the information sheets referred to in the medical information letter were provided.

PANEL RULING

The Panel noted that both parties agreed that the letter at issue had been sent by Boehringer Ingelheim's medical information department to a health professional. Boehringer Ingelheim submitted that the letter could take the benefit of the exemption to the definition of promotion set out in Clause 1.2; it was a non-promotional response to an unsolicited enquiry from a health professional. The Panel noted that to take the benefit of the exemption the response to an unsolicited enquiry must not be promotional, go beyond the ambit of the original enquiry or be misleading; the response must be accurate. The recipient of the letter at issue wished to remain anonymous and so Boehringer Ingelheim was unable to identify the original enquiry. Boehringer Ingelheim submitted that the request for information would have arisen during the course of a representative visit. Bayer, however, alleged that the letter at issue was sent proactively to the health professional, an orthopaedic surgeon, and potentially to many other health professionals. The Panel noted that the burden fell on Bayer to establish its case on the balance of probabilities. The Panel noted that Bayer had submitted no evidence to support its submission that the letter at issue was a circular mailing. The Panel considered that the position was complicated in that Boehringer Ingelheim had not been provided with the name of the recipient of the letter and its author had left the company. The Panel noted that Boehringer Ingelheim acknowledged that it needed to improve the level of detail it recorded for each request. Thirteen responses, sent between 1 January and 18 February 2009, to requests via representatives for information on the comparisons of bleeding and other data between rivaroxaban and dabigatran had been identified by Boehringer Ingelheim. In the Panel's view particular care needed to be taken when requests for information resulted from a meeting with a representative. Companies wishing to take the benefit of the exemption to the definition of promotion had to be able to demonstrate that the request was unsolicited.

The Panel noted that Bayer had commented on the use of the brand name in the letter. The use of the brand name did not necessarily mean that the letter was promotional and thus could not take the benefit of the exemption to Clause 1.2. Equally the use of the generic name did not necessarily mean the letter was non-promotional.

The Panel noted that Bayer had alleged a breach of Clause 1.2. The Panel noted that Clause 1.2 was an explanatory clause which set out, *inter alia*, the definition of promotion, examples of promotional activity and material and exemptions to the definition of promotion. It was not a clause which was capable of infringement. The Panel thus made no ruling on all of the alleged breaches of Clause 1.2 at point 1.

The Panel noted Boehringer Ingelheim's submission about the scope of the original enquiry. The letter at issue began 'I understand that you are carefully considering the available oral agents for VTE thromboprophylaxis in patients undergoing hip or knee replacement surgery. I wish to take this opportunity to update you with the information that has become available'. The Panel considered that it was not unreasonable to assume that this paragraph reflected the original enquiry.

The Panel noted that Pradaxa was licensed for the primary prevention of venous thromboembolic events in adult patients who had undergone elective total hip replacement surgery or total knee replacement surgery. The penultimate paragraph of the letter at issue headed 'Ongoing studies' discussed the relatively early publication of the Pradaxa study in SPAF (stroke prevention in arterial fibrillation) compared to SPAF studies of all other new anticoagulants. This was the first mention of SPAF in the letter. Pradaxa was not licensed for SPAF. The Panel noted all its comments above about the status of the letter and whether it could take the benefit of the exemption to the definition of promotion set out in Clause 1.2 of the Code. It was unclear whether the enquiry was solicited or unsolicited. The Panel considered that, on the balance of probabilities, by including the reference to SPAF, the letter might well have gone beyond the scope of the original enquiry outlined at the beginning of the letter which meant that it could not take the benefit of the exemption in Clause 1.2 to the definition of promotion. The Panel considered that the letter promoted Pradaxa for an unlicensed indication and was inconsistent with the particulars listed in its summary of product characteristics (SPC). A breach of Clause 3.2 was ruled.

The Panel did not consider that the reference to the unlicensed indication represented a breach of Clause 2 as alleged which was reserved as a sign of particular censure. No breach of Clause 2 was ruled.

The Panel noted that Bayer had alleged a breach of undertaking in relation to Boehringer Ingelheim's failure to comply with an inter-company agreement about references to Pradaxa and SPAF. The Panel noted that Clause 25 applied solely to undertakings given to the Authority in relation to rulings made under the Code. It did not apply to agreements reached during inter-company dialogue. No breach of Clause 25 was ruled.

The Panel noted that the introductory section of the letter referred to the misconception that LFT monitoring was necessary with Pradaxa and stated that the recommendation for Pradaxa was that a one-off baseline ALT measurement be made during the pre-operative assessment. The letter also stated that this one-off measurement to assess the patient should not typically require the taking of additional blood over and above usual routine and that 'Importantly any subsequent LFT testing or LFT monitoring is not required for Pradaxa'. The Panel noted Boehringer Ingelheim's submission that routine pre-operative work normally included venepuncture for blood chemistry and haematology; if LFT testing was not normally included it could be added without the patient giving additional blood. The Panel did not consider that the section at issue gave the misleading impression that measurement of LFTs was part of the routine pre-operative work defined by NICE as alleged. NICE was not mentioned at all in the letter. No breach of Clauses 7.2 and 7.4 was ruled. Neither did the Panel consider that the section was misleading as to Pradaxa's safety profile as alleged or incapable of substantiation in this regard. The section discussed the one-off baseline ALT assessment. Adverse events subsequent to administration of Pradaxa was a separate matter. Hepatobiliary disorders occurred in less than 1% of patients. No breach of Clauses 7.2, 7.4 and 7.9 was ruled.

The Panel noted that the section entitled 'Balance between efficacy and bleeding' explained that for all new oral anticoagulants there was a need for a balance between efficacy and bleeding risk. It continued 'There is some concern as to whether the superior efficacy achieved by Xarelto (rivaroxaban) was at the cost of increased bleeding risk'. This was followed by a reference to an enclosed summary of the rivaroxaban pooled RECORD study data which included pooled bleed data which showed significance. Bayer stated that it had not been provided with a copy of the summary following a request to Boehringer Ingelheim.

The Panel noted that the review by Frostick discussed the RECORD 1, 2 and 3 studies wherein rivaroxaban was compared with enoxaparin. It was noted that there was no head-to-head comparison of dabigatran and rivaroxaban; Pradaxa and rivaroxaban had each been compared to enoxaparin in separate non-inferiority studies wherein the safety profiles of each showed no statistically significant between group difference. The author concluded that the safety data seemed to indicate that rivaroxaban might be associated with a greater risk of bleeding (as shown in the pooled data analysis of RECORD 1, 2, 3 and 4) and that the increased bleeding risk could be a major disadvantage.

The Panel also noted that NICE guidance 170 commented on the RECORD data noting that rivaroxaban at 10mg daily might be more efficacious than enoxaparin in preventing VTE but this was accompanied by a small increased risk of major bleeding. The NICE guidance included reference to indirect comparison of dabigatran and rivaroxaban. The Committee agreed that on balance rivaroxaban and dabigatran had broadly similar efficacy profiles and noted the need to balance prevention of VTE with possible adverse effects particularly the incidence of major bleeds.

Attached to the letter at issue was, *inter alia*, a pooled analysis of the four RECORD studies based on a presentation by Turpie (2008) and a bleeding definition paper. The RECORD studies each investigated rivaroxaban for the prevention of venous thromboembolism in patients undergoing major orthopaedic surgery vs enoxaparin. The pooled analysis concluded that for the total treatment duration significantly more bleeding was seen with rivaroxaban than enoxaparin for the combined category major bleeding plus clinically relevant non-major bleeding. The published abstract Turpie (2008) concluded, *inter alia*, that rivaroxaban was not associated with a statistically significant increase in the risk of major bleeding. The Panel noted Bayer's submission that only one of the Bayer composite endpoints for bleeding reached significance and only at a single time point that included patients receiving placebo vs rivaroxaban in RECORD 2. Boehringer Ingelheim data on file analysed the bleeding definitions and bleeding rates in the REVOLUTION study programme (Pradaxa) compared to RECORD and noted that a decision was made to change the bleeding definition for the RECORD phase III programme which could be directly responsible for the low overall events rates within the major bleeding category reported in the clinical trials.

The Panel noted that the claim 'There is some concern as to whether the superior efficacy achieved by Xarelto was at the cost of increased bleeding risk' in the letter at issue would be read as a direct comparison with Pradaxa and this was not so. The RECORD studies compared rivaroxaban with enoxaparin. There was only indirect comparative data for Pradaxa and Xarelto. The letter had not provided sufficient detail about the comparisons and was thus disparaging. A breach of Clause 8.1 was ruled.

The Panel considered that the letter by stating without further explanation that the pooled bleed data 'shows significance' over simplified the position and gave a misleading impression of the totality of the bleed data. The Panel noted that whilst further information about bleeding rates was given in the attachments to the letter at issue, the letter must be capable of standing alone with regard to the requirements of the Code. A breach of Clause 7.2 was ruled. On balance, the Panel did not consider that the reference to significance was disparaging as alleged. No breach of Clause 8.1 was ruled.

The Panel did not consider that the failure to discuss the efficacy of rivaroxaban as demonstrated in the RECORD studies was misleading or disparaging as alleged. The letter made it clear that rivaroxaban achieved superior efficacy. No breach of Clauses 7.2 and 8.1 was ruled. Consequently the Panel ruled no breach of Clause 9.1.

The Panel noted Boehringer Ingelheim's submission that medical information was rarely asked about the relative efficacy of rivaroxaban and Pradaxa. The letter referred to the balance between efficacy and bleeding it did not detail the products' relative efficacy and thus the Panel did not consider that the failure to refer to the REMOBILIZE study was misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel noted the section headed 'Epidural catheters' stated that their insertion/removal in the presence of an anticoagulant needed careful consideration and referred to an enclosed information sheet. The Panel noted that Section 4.4 of the Pradaxa SPC stated that Pradaxa was not recommended for use in patients undergoing anaesthesia with post-operative indwelling epidural catheters. The Panel noted that whilst this cautionary wording was reflected in the information which accompanied the letter, the letter had to be able to stand alone as regards the requirements of the Code. An otherwise misleading claim could not be qualified in an accompanying document. The Panel considered that given the wording of the SPC the letter was misleading about the concomitant use of catheters and the administration of Pradaxa and inconsistent with the particulars listed in its SPC. Breaches of Clauses 3.2 and 7.2 were ruled.

The Panel noted that its rulings of breaches of the Code outlined above demonstrated that the letter was, in part, inaccurate and misleading were further reasons why the letter could not take the benefit of the exemption to Clause 1.2.

The Panel noted that Bayer had also alleged a breach of Clause 9 as the letter as a whole was promotional in tone throughout and not an objective statement of medical information. The Panel considered that health professionals and others should be able to rely upon medical information departments as a source of objective information about products. The Panel noted its rulings of breaches of the Code and the Panel considered that the letter as a whole failed to maintain high standards. A breach of Clause 9.1 was ruled.

2 British Society for Haematology, 49th Annual Scientific Meeting, April 2009

COMPLAINT

Bayer alleged that Boehringer Ingelheim's stand at this meeting promoted ongoing clinical trials of dabigatran in unlicensed indications, including life

size trial logos in brand colours. Bayer alleged a breach of Clause 3.2 because it was not in accordance with the terms of the Pradaxa marketing authorization. Furthermore the safety and efficacy data for these trials were not yet available.

Bayer alleged that this provision of information about clinical trials was promotional in nature in breach of Clauses 4, 12.1 and 21.3. Having regard to this and Clause 3.2 this activity brought discredit upon the industry and was thus in breach of Clause 2. Photographs of the stand were provided.

RESPONSE

Boehringer Ingelheim stated that it had two stands at the meeting. One, which promoted Pradaxa, was set up and operated by sales and marketing. The second stand, which was the subject of this complaint, was located entirely separately within the exhibition hall and was set up and operated exclusively by medical affairs and medical information department. This second, non-promotional stand, carried no product branding and referred to only to the generic name dabigatran etexilate. It carried a clear statement of the approved indication for dabigatran and displayed study logos of the clinical studies of most interest to haematologists. Copies of the stand panels for this non-promotional stand were provided.

Boehringer Ingelheim disagreed with Bayer's allegation that the stand promoted unlicensed indications for dabigatran in breach of Clause 3.2 or that the information about clinical trials was promotional in breach of Clauses 4, 12.1 and 21.3. Boehringer Ingelheim maintained its view that the stand was appropriate and provided information on dabigatran studies to this group of health professionals in a way which complied with the Code. Haematologists were highly interested in the available data and ongoing development of oral anticoagulants in disease areas beyond VTE prophylaxis because of the burden of work that warfarin management placed upon their departments. The stand providing scientific information was set up precisely to address this anticipated demand and was located to ensure that such information was provided separately from the promotion of Pradaxa within its licensed indication. Only interested clinicians would visit and seek information. Information was provided exclusively by medical department personnel. Delegates with questions on development and clinical study matters could be directed to the medical stand from the Pradaxa promotional stand but promotional personnel were expressly forbidden from escorting the delegates to the medical stand.

Boehringer Ingelheim submitted that while the stand carried very brief information and logos for the major studies that haematologists might be interested in, it made no promotional statements about these. The personnel on the stand provided only factual scientific information related to dabigatran including information on the scope, design and progress of ongoing studies. Boehringer Ingelheim strongly believed that this provided a scientifically valid and useful service for these clinicians that was not promotion of dabigatran. The logos and text displayed on the stand and the information that was provided in response to enquiries was, in Boehringer Ingelheim's view, directly comparable to the information provided to health professionals through the medium of a sponsored scientific symposium. The Bayer allegation that this constituted promotion of an unlicensed indication was unsustainable.

PANEL RULING

The Panel noted that the Code did not prevent the legitimate exchange of medical and scientific information during the development of a medicine provided that any such information or activity did not constitute promotion prohibited by Clause 3 or any other clause. In the Panel's view companies needed to be particularly careful when providing medical and scientific information about unlicensed indications.

The Panel noted that Boehringer Ingelheim had two stands, one that was clearly promotional and the stand at issue which was located entirely separately in the exhibition hall. The actual meeting was run by the British Society for Haematology; Boehringer Ingelheim like many companies had paid for exhibition space.

The Panel noted that the exhibition stand at issue presented information about the REVOLUTION clinical trial programme: acute VTE treatment; secondary VTE prevention; SPAF and secondary prevention of cardiac events in patients with acute coronary syndrome. The Panel noted the submission that the stand had been set up to meet an anticipated demand for information beyond VTE prevention. The Panel disagreed with the submission that only interested physicians would visit and seek information. The stand panels included a section listing features of dabigatran, a reference to what appeared to be a Boehringer Ingelheim meeting 'A Question of Anticoagulation' and stated that medical information was available on request. In the Panel's view such a statement would solicit requests. Boehringer Ingelheim submitted that the logos used on the stand were for the clinical studies mentioned and no product branding was included. The stand was manned by medical affairs and medical information staff. Boehringer Ingelheim had provided the briefing document to the sales team regarding UK congresses which stated that the REVOLUTION stand was used in addition to the normal branded stand pre-launch.

The Panel was concerned about the stand; its presence demonstrated a poor understanding of the requirements of the Code. The Panel noted that the supplementary information to Clause 1.2 provided relevant guidance stating that a solicited enquiry would be one where a company invited a person to

make a request. Placing documents on an exhibition stand amounted to an invitation to take them. The Panel considered that the exhibition stand at issue solicited enquiries about dabigatran and the REVOLUTION clinical trial programme. The Panel noted that Pradaxa was licensed for the primary prevention of VTE following elective total hip or total knee replacement surgery. The Panel considered that the exhibition stand promoted Pradaxa for unlicensed indications and this was inconsistent with the SPC. A breach of Clause 3.2 was ruled. As Pradaxa was promoted prescribing information needed to be provided or made available at the stand. A breach of Clause 4.1 was ruled. The Panel did not consider that the promotional activity was disguised as alleged. No breach of Clause 12.1 was ruled. The Panel did not consider that the stand at issue represented a failure to disclose details of clinical trials as required by Clause 21.3. The supplementary information to that clause reminded companies that such information must not constitute promotion. That aspect was covered by the Panel's rulings outlined above. No breach of Clause 21.3 was ruled.

Although seriously concerned about the stand, on balance the Panel did not consider that a ruling of a breach of Clause 2 was warranted. This was reserved for use as a sign of particular censure. No breach of Clause 2 was thus ruled.

Complaint received **18 May 2009**

Case completed **14 September 2009**

CONSULTANTS IN CHILD AND ADOLESCENT PSYCHIATRY v LILLY

Strattera Support Service

Two consultants in child and adolescent psychiatry complained jointly about a Strattera (atomoxetine) Support Service offered by Lilly and drew attention to a letter from the company which asked them to recruit their patients to the service.

The complainants alleged that the service involved pharmaceutical company employees having direct contact with patients to support carers of patients taking Strattera in the early phases; this was totally inappropriate. Such support should be provided by their clinicians and the complainants provided that support. The complainants were concerned that if pharmaceutical company employees had direct contact with the patients they would give them inappropriate and biased advice about the company's product.

The detailed response from Lilly is given below.

The Panel noted that it was not necessarily a breach of the Code for a pharmaceutical company to have direct contact with patients taking its medicines. Pharmaceutical companies had to ensure that prescription only medicines were not advertised to the public. Information about prescription only medicines made available to the public had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product.

The Panel noted that the letter at issue introduced the Strattera Support Service as an initiative for supporting carers of children and adolescents prescribed Strattera for attention deficit hyperactivity disorder (ADHD) during the first 12 weeks of treatment. It was stated that the service was a Lilly initiative delivered in conjunction with a named service provider. The Panel queried whether the recipients would know who or what the service provider was. A patient/carer information sheet accompanying the letter referred to the delivery of the service by independent nurses and stated that the service was not intended to replace their doctor's advice or the package leaflet provided with the medicine. Neither the letter nor the accompanying patient/carer information sheet, however, made it abundantly clear that neither Lilly nor its representatives would have any direct patient contact. The letter stated that the service would offer telephone support for carers and patients, with a mutually agreed frequency. Neither the letter nor the patient/carer information sheet mentioned the follow-up calls at 6, 9 and 12 months referred to in Lilly's response. Lilly had submitted that the frequency of proactive and reactive contact was based on carer/patient needs, the requirements for which were discussed at first contact between the nurse and carer.

There were two referral routes. The first was initiated by clinicians who, having been introduced to the service by representatives and expressed an interest in it were followed-up by a manager or nurse employed by the service provider. The clinician would complete a service authorization document and thereafter refer patients who had been prescribed Strattera to the service. The patient/carer would then have to complete a consent form before they could be enrolled. The alternative route was patient initiated via pharmacies whereby a retail pharmacist could give the patient/carer a letter which explained how the service worked and provided a contact number. As above the clinician would still have to have signed the service authorization document and agreed to the patient being enrolled into the service before it could be delivered.

The information sheet provided to patients/carers described the service and made it clear that it worked alongside and did not replace doctor's advice and was provided by independent nurses. There was a clear declaration of sponsorship by Lilly.

The Panel noted that the service was designed to support patients and their carers. As a result of this service no gift, benefit in kind or pecuniary advantage was offered or given to members of the health professions as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. No breach of the Code was ruled.

The Panel noted that contrary to the complainants' allegation, Lilly employees had no direct contact with patients. All patient/carer contact was with a nurse employed by the service provider. Any data collected was aggregated and anonymised before being seen by Lilly. The Panel did not consider that the service and letter provided to patients was inappropriate or otherwise biased as alleged. The patient/carer was only told about the service once the prescribing decision was made and thus the provision of the service did not encourage them to seek a prescription for Strattera. No breach of the Code ruled.

During its consideration of this case the Panel observed that health professionals were sometimes concerned that pharmaceutical company

employees might have direct contact with patients via various service offerings. The Panel considered that, in introducing and describing their service offerings to health professionals, it would be helpful if companies made the position with regard to patient contact abundantly clear at the outset. Whilst companies were familiar with names of third party service providers, health professionals might not be.

Two consultants in child and adolescent psychiatry complained jointly about a Strattera (atomoxetine) Support Service offered by Lilly.

COMPLAINT

The complainants referred to a letter from Lilly which asked them to recruit their patients to the Straterra Support Service. The complainants alleged that the service involved pharmaceutical company employees having direct contact with patients to support carers of patients taking Strattera in the early phases.

The complainants considered that it was inappropriate for pharmaceutical company employees to have direct contact with patients. Such support when people took medicines should be provided by their clinicians and the complainants provided that support. The complainants were concerned that if pharmaceutical company employees had direct contact with the patients they would give them inappropriate and biased advice about the company's product.

When writing to Lilly the Authority asked it to respond in relation to Clauses 2, 9.1, 18.1 and 22.2 of the Code.

RESPONSE

Lilly considered that there had been a complete misunderstanding of how the Strattera Support Service operated.

The Strattera Support Service was a non-promotional programme provided by a service provider on behalf of Lilly. It was designed to provide telephone support to carers of children and adolescents with attention deficit hyperactivity disorder (ADHD) after the prescriber had decided to start the patient on Strattera. The service covered the first twelve weeks of therapy, with follow-up calls made at 6, 9 and 12 months. The frequency of proactive and reactive contact was based on carer/patient needs and requirements which were discussed at the first contact. The Strattera Support Service nurse was available during normal office hours.

Lilly submitted that from its national roll out in May 2008, the Strattera Support Service had been introduced to clinicians by its representatives. The representatives only gave a brief description of the service (in accordance with Clause 18), and if the clinician was interested in the service, all subsequent follow-up was carried out by the Strattera Support Service manager or one of the Strattera Support Service nurses, working for a service provider on behalf of Lilly. If the clinician wanted their patients to access the service they had to complete the Service Authorisation document and return it to the service provider. When this was completed the clinician could refer patients to the service.

When a clinician referred a patient into the service, a consent form had to be completed by the carer/patient before the Strattera Support Service nurse could enrol that carer into the service.

Therefore, a patient/carer could not be enrolled into the Strattera Support Service without the explicit consent of their clinician and the carer/patient, in each case after the patient had been prescribed Strattera.

As of 1 June 2009 patients could also be referred to the Strattera Support Service via a number of UK retail pharmacies which ran software linked to a database. When a pharmacist in such a pharmacy dispensed Strattera, additional information about the Strattera Support Service appeared on the screen, including a letter that could be printed off and given to the patient/carer. The letter explained how the Strattera Support Service worked and included the telephone number of a secure voicemail at the service provider. If a patient/carer telephoned this number to be enrolled in the service, the Strattera Support nurse would check if that patient's clinician had already signed up to the service. If they had, the nurse would obtain patient/carer consent. If the clinician had not previously signed up, the nurse would require the clinician to complete the Service Authorisation document as above. Once again, as above, the clinician had to sign the patient up to the programme before it could be initiated.

Lilly submitted that the letter at issue was sent to consultant and associate specialists in paediatrics and child and adolescent psychiatry as well as nurses with an interest in ADHD and consultants in learning difficulties. Lilly ensured that its mailing list did not contain the details of those who did not wish to receive promotional mailings from pharmaceutical companies.

Lilly submitted that the manager and the nurses recruited to work on this programme were all registered with the Nursing and Midwifery Council and as such were bound to its code of conduct. The manager and the nurses were all on the mental health part of the register and had experience of working in this area both in the NHS as well as with the service provider.

During the initial telephone call to the carer/patient, the Strattera Support Service nurses assessed the level of support that would be required. The nurse would telephone the carer/patient at mutually agreed intervals and the carer/patient could

telephone the nurse during office hours. The nurse's role was to provide support through the initial side effects that might occur on Strattera treatment. Any adverse reactions were reported to Lilly according to its standard operating procedures. Any data collected by the nurses was transmitted live to a secure server owned by the service provider and kept confidential.

The representative's role was limited to setting up initial appointments for the Strattera Support Service nurses – subsequent follow-up was carried out by the nurses themselves. Any data collected were aggregated and anonymised before being seen by Lilly. None of the service provider's payment for providing the service was contingent upon the generation of Strattera prescriptions.

Lilly submitted that the Strattera Support Service conformed to all aspects of the Code.
The service presented information to patients or carers in a factual and balanced way. Patients would only be enrolled after a decision had been made to prescribe Strattera and thus there could be no suggestion that members of the public were being encouraged to use or ask for Strattera. The Patient Consent Form was included to demonstrate that the programme was described in a factual and balanced way.

With regard to Clause 18.1, Lilly submitted that health professionals were not given any inducements to prescribe Strattera or sign patients up to the service. High standards had been maintained throughout with the service being conducted by professionally qualified nurses who had experience in mental health. The service provider maintained good standards, and all data that Lilly received had been anonymised. The company denied a breach of Clause 9.1. Lilly further submitted that as the Strattera Support Service met all the conditions of the Code no breach of Clause 2 had taken place.

In summary Lilly submitted that this case had arisen because the complainants did not understand how the Strattera Support Service was run: the service benefited patients and was run appropriately by a third party on behalf of Lilly, fully within the Code.

PANEL RULING

The Panel noted that it was not necessarily a breach of the Code for a pharmaceutical company to have direct contact with patients taking its medicines. Pharmaceutical companies had to ensure that prescription only medicines were not advertised to the public. Information about prescription only medicines made available to the public had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product (Clauses 22.1 and 22.2).

The Panel noted that the letter at issue introduced the Strattera Support Service as an initiative for supporting carers of children and adolescents prescribed Strattera for ADHD during the first 12 weeks of treatment. It was stated that the service was a Lilly initiative delivered in conjunction with a named service provider. The Panel queried whether the recipients would know who or what the named service provider was. A patient/carer information sheet accompanying the letter referred to the delivery of the service by independent nurses and stated that the service was not intended to replace their doctor's advice or the package leaflet provided with the medicine. Neither the letter nor the accompanying patient/carer information sheet, however, made it abundantly clear that neither Lilly nor its representatives would have any direct patient contact. The letter stated that the service would offer telephone support for carers and patients, with a mutually agreed frequency. Neither the letter nor the patient/carer information sheet mentioned the follow-up calls at 6, 9 and 12 months referred to in Lilly's response. Lilly had submitted that the frequency of proactive and reactive contact was based on carer/patient needs, the requirements for which were discussed at first contact between the nurse and carer.

There were two referral routes into the service. The first was initiated by clinicians who, having been introduced to the service by representatives and expressed an interest in it were followed- up by a manager or nurse employed by the service provider. The clinician would complete a Service Authorization document and thereafter refer patients who had been prescribed Strattera to the service. The patient/carer would then have to complete a consent form before they could be enrolled. The alternative route was patient initiated via pharmacies whereby a retail pharmacist could give the patient/carer a letter which explained how the service worked and provided a contact number to enrol on the service. As above the clinician would still have to have signed the Service Authorization document and agreed to the patient being enrolled into the service before the service could be delivered.

The information sheet provided to patients/carers described the service and made it clear that it worked alongside and did not replace doctor's advice and was provided by independent nurses. There was a clear declaration of sponsorship by Lilly.

The Panel noted that the service was designed to support patients and their carers. As a result of this service no gift, benefit in kind or pecuniary advantage was offered or given to members of the health professions as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. No breach of Clause 18.1 was ruled.

The Panel noted that contrary to the complainants' allegation, Lilly employees had no direct contact with patients. All patient/carer contact was with a nurse employed by the service provider. Any data collected was aggregated and anonymised before

being seen by Lilly. The Panel did not consider that the service and letter provided to patients was inappropriate or otherwise biased as alleged. The patient/carer was only told about the service once the prescribing decision was made and thus the provision of the service did not encourage them to seek a prescription for Strattera. No breach of Clause 22.2 was ruled.

The Panel noted its rulings above and consequently ruled no breach of Clauses 9.1 and 2.

During its consideration of this case the Panel observed that health professionals were sometimes concerned that pharmaceutical company employees might have direct contact with patients via various service offerings. The Panel considered that, in introducing and describing their service offerings to health professionals, it would be helpful if companies made the position with regard to patient contact abundantly clear at the outset. Whilst companies were familiar with names of third party service providers, health professionals might not be.

Complaint received **18 June 2009**

Case completed **3 August 2009**

CASE AUTH/2244/6/09

GENERAL PRACTITIONER AND PHARMACIST v STIEFEL

Promotion of Duac

A general practitioner and a pharmacist jointly complained about the promotion of Duac Once Daily Gel (clindamycin 1% and benzoyl peroxide 5%) by Stiefel. The materials at issue were a GP leavepiece; a pharmacist leavepiece; two journal advertisements; two abbreviated advertisements and a GP Review, January 2008, Management of mild and moderate acne vulgaris. Duac was indicated for the treatment of mild to moderate acne vulgaris, particularly inflammatory lesions.

The detailed response from Stiefel is given below.

One of the complainants telephoned Stiefel's medical information department on 29 May to ask for copies of references cited in the Duac promotional materials: The company was not cooperative: The medical information person could not give an assurance that she could provide the cited data-on-file as it might not be available. After much insistence and reference to the Code, the complainant was finally assured that the request would be treated as urgent. Over two weeks later the information had not been received.

The Panel noted that there was disagreement as to what had been requested. It was impossible to know what exactly transpired between the parties. Nonetheless two cited references had been posted one week after the initial request for papers. Unfortunately the house number recorded on the telephone enquiry report was wrong by one digit and thus the package was returned to Stiefel marked 'addressee unknown'. It was unfortunate that the wrong address had been recorded however, in the Panel's view, such an error did not constitute a breach of the Code. References had been posted in a timely manner and so no breach of the Code was ruled. This was upheld by the Appeal Board following an appeal by the complainants.

The complainants alleged that the GP leavepiece was inconsistent with the indication of Duac Once Daily Gel, in that it depicted an acne grading chart which featured not only inflammatory lesions but also, non-inflammatory and nodulocystic lesions. That the chart featured severe lesions misleadingly implied that Duac could be used for other than mild to moderate acne.

The Panel considered that Duac an acne grading chart showing all the grades of acne was useful so that a prescriber could tell when the condition was too severe to be treated with Duac. Nonetheless, if all grades of acne were to be shown, prescribers must be very clearly informed of when to use Duac; in that regard the Panel considered that a double-headed arrow spanning the pictures of mild to moderate acne and the statement in the prescribing information that Duac was for mild to moderate acne were insufficient. Some readers might assume that Duac could be used for severe acne. The Panel considered that the leavepiece was inconsistent with the particulars listed in the Duac summary of product characteristics (SPC). A breach of the Code was ruled. The Panel further considered that the leavepiece was misleading about the product's licensed indication and in that regard did not encourage the rational use of Duac. Breaches of the Code were ruled.

The complainants alleged that the claim in the leavepieces, referenced to Langner *et al* (2007), that 'Duac Once Daily Gel works fast' was misleading, exaggerated, could not be substantiated and was inconsistent with the SPC. The SPC stated that patients should be advised that in some cases 4-6 weeks of treatment might be required before the full therapeutic effect was observed. Langner *et al* (2007) did not substantiate the claim.

The Panel noted that Langner *et al* (2007) was a comparison of Duac and Zineryt in the treatment of mild to moderate facial acne. The claim at issue, however, was not comparative and did not compare Duac's efficacy or time to onset of action with that of Zineryt. Langner *et al* (2007) showed that from week 0 to week 1, the total number of non-inflammatory lesions in patients treated with Duac (n=73) fell from a mean of 53.4 to 41.8, similarly the mean total number of inflammatory lesions fell from 34.3 to 27.9 and the mean total number of lesions fell from 87.7 to 69.7. Over 20% of patients treated with Duac showed at least a 30% reduction in total lesion counts at week 1 and over 60% showed at least a 30% reduction in total lesion counts at week 2. The Panel considered that the claim 'Duac Once Daily Gel works fast' was not misleading or exaggerated as alleged. No breach of the Code was ruled. The claim had been substantiated and so no breach of the Code was ruled. The Panel did not consider that the claim was inconsistent with the SPC as alleged. No breach of the Code was ruled.

Upon appeal by the complainants the Appeal Board noted that the audience (GPs and pharmacists) would be familiar with the treatment of acne, and would consider that a topical treatment which showed results after one to two weeks would be considered as acting 'fast'. The Appeal Board noted that Luckey *et al* (2007) concluded that an acne treatment acted fast because a significant effect was observed at week 4. Teenagers would want to know that they could expect to see a positive

response to therapy after a week or so. In this regard the Appeal Board noted that it would take much longer before oral therapies were seen to have an effect. The Appeal Board did not consider that health professionals would be misled as to assume that the claim implied that the full therapeutic effect of Duac would be achieved 'fast'.

The Appeal Board considered that the claim 'Duac Once Daily Gel works fast' was not misleading or exaggerated as alleged, it had been substantiated and was not inconsistent with the SPC as alleged. The Appeal Board upheld all of the Panel's rulings of no breach of the Code.

The claim that Duac was 'cosmetically acceptable' appeared in the leavepieces and was referenced to data on file (2001). The complainants alleged that the data on file was not in the public domain and had not been provided on request. It was not up-to-date and one could reasonably surmise that it was unlikely to substantiate the claims of cosmetic acceptability for the modern teenagers depicted in the leaflets. It was also very likely that today's teenagers had a very different perspective compared with the prevalent view in 2001. The claim of cosmetic acceptability focused entirely on the teenagers' need to look good and not silly. However, the latter ignored the occurrence of important side-effects which also needed to be balanced whilst pursuing aesthetics. The emphasis on cosmetic acceptability, particularly with regard to the face as opposed to other equally important parts of the body was not only inconsistent with the SPC but also tantamount to suggesting that Duac was used as a cosmetic.

The Panel noted that the data on file compared the consumer acceptability of Clindoxyl Gel [similar to Duac] and Benzamycin gel on the basis of immediate perception of aesthetic attributes and after one week's use. Patients (n=51) were asked to rate smell, colour and feel on the skin in terms of greasiness, granularity, spreadability, and whether a residue/film was left; they were also asked if they had experienced stinging and to rate the ease of applying make-up after applying the product to their skin. Subjects preferred Clindoxyl Gel over Benzamycin on virtually each attribute and on an overall basis.

The Panel noted that the complainants had not seen the data on file and had complained that, *inter alia*, results from 2001 would not be relevant to teenagers in 2009. No rationale was provided for this argument. The Panel did not consider that the claim was misleading in that regard and no breach of the Code was ruled. The Panel considered that on the basis of the results of the consumer acceptability study, it was not unreasonable to claim that Duac Once Daily Gel was cosmetically acceptable. The claim was not misleading and had been substantiated. No breaches of the Code were ruled. The Panel did not consider that the claim was tantamount to suggesting that the product was a cosmetic. In that regard the claim encouraged the rational use of the medicine. No breach of the Code was ruled.

The complainants noted that the GP leavepiece claimed that Duac Gel got on with teenagers. This claim of efficacy appeared to be unsubstantiated. Langer *et al* (2007) did not substantiate the claim as the mean age was 21.2 years in the Duac arm of the study.

The Panel noted that in Langner *et al* (2007) patients in the Duac group were aged 12-38, mean age of 21.2 years. There was no data before the Panel which suggested that efficacy differed according to the age of the patient.

In the GP leavepiece the headline 'Duac Once Daily Gel gets on with teenagers' was followed by a number of claims regarding the ease of use/acceptability of Duac eg once daily application, odour free etc. The Panel further noted, from above, that the majority of patients had at least a 30% decrease in total lesion count at two weeks. In the Panel's view this onset of action time would encourage compliance in a group where compliance was likely to be difficult. On balance the Panel considered that the claim 'Duac Once Daily Gel gets on with teenagers' had been substantiated. No breach of the Code was ruled.

The claim 'Teenagers are "busy" Duac is a once daily gel' appeared in both leavepieces. One advertisement stated 'Once a day is good, because they're, like, so busy'. The advertisement and the pharmacist leavepiece also featured the claim 'can be worn under make-up'. The complainants alleged that the issue of convenience was overstated given that the SPC clearly stated that the gel should be applied once daily in the evening to affected areas after the skin had been thoroughly washed, rinsed with warm water and gently patted dry. The complainants were not sure that this strict regimen was consistent with the ease of use implied by the unqualified once daily application claim in support of the use of Duac for teenagers who were impatient and busy. The claim that Duac could be used under make-up might be of relevant to young teenagers, however in the early phase of treating moderate acne it was generally accepted that cosmetics should be avoided in order to detect side effects and particular cosmetic products should be avoided all together. The focus on an early response aligned with less than helpful and unqualified generalisations regarding the use of cosmetics was misleading.

The Panel noted that Duac should be applied once daily in the evening, to affected areas after the skin had been thoroughly washed, rinsed with warm water and gently patted dry. The Panel did not consider that this was a strict regime as alleged or that it imposed restrictions on 'busy' teenagers. No breach of the Code was ruled.

With regard to wearing make-up, the Panel noted that the Duac SPC stated that cosmetics that had a

strong drying effect, and products with high concentrations of alcohol and/or astringents, should be used with caution as a cumulative, irritant effect might occur. There was no clinical data before the Panel to support the concomitant use of make-up. The Panel considered that the claim 'can be worn under make-up' did not reflect the evidence and was misleading in that regard. A breach of the Code was ruled.

The complainants alleged that the claim 'No need to keep it in the fridge' in the GP leavepiece was incomplete and therefore misleading. The storage of conditions prior to dispensing [store in a refrigerator at 2-8ºC] were important and had been omitted; this information was relevant to both pharmacists and dispensing GPs.

The Panel noted that the leavepiece at issue was specifically for non-dispensing prescribers. The claim 'No need to keep it in the fridge' appeared as the fourth bullet point on a page headed 'Duac Once Daily Gel gets on with teenagers'. In the context in which it appeared the Panel considered that the claim was about the patient's use of Duac, not the dispenser's storage of the product and so no breach of the Code was ruled.

The complainants alleged that the claim in the advertisement that 'Duac … starts working within a week' was misleading and unsubstantiated. Langner *et al* (2008) cited in support was a small, single-blind study which did not represent the balance of evidence in respect of the speed of onset of action of Duac. Specifically the comparison was with Differin Gel and in that regard the claim should be qualified as it might not be relevant with other topical treatments.

The Panel considered data to substantiate the claim that Duac 'starts working within a week' would have to show that the product was effective in less than seven days. The Panel had no such data before it. Both Langner *et al* (2007) and (2008) reported efficacy at week one but not before then. The Panel thus considered that the claim was misleading and had not been substantiated; breaches of the Code were ruled. The Panel considered that the claim was about Duac alone; it was not a comparison with Differin Gel or any other product. In that regard the Panel did not consider that the claim was a misleading comparison as alleged and no breach of the Code was ruled.

The complainants alleged that the advertisement also appeared to imply that the speed of onset of action and effectiveness of Duac improved teenagers' confidence with particular reference to facial acne rather than lesions on other parts of the body to such an extent that patients could stop hiding under their hoodies within one week. The latter was clearly a generalisation and inconsistent with the SPC which did not indicate that Duac was specifically effective in the management of facial acne over and above lesions on other parts of the body. The promotion of this aspect of the benefits of Duac was exaggerated and distorted the premise for rational prescribing.

The Panel did not consider that the advertisements implied that Duac was particularly effective for facial acne as opposed to acne on any other part of the body. In the Panel's view the advertisements depicted a typical acne patient. The Panel did not consider that the advertisements inappropriately exaggerated or distorted the premise of rational prescribing as alleged. No breach of the Code was ruled.

The Acne Working Group GP Review January 2008 was cited in support of general claims about acne in the pharmacist leavepiece. The complainants stated that it was evident that the Acne Working Group was convened at the behest of Stiefel which was close to the discussions and in control of the outputs. The cover of the article looked like the independent parent journal, GP, and this in conjunction with the statement that the review was provided as a service to medicine by Stiefel misled because it implied that it was not promotional. Promotional claims for Duac were principally about the importance of benzoyl peroxide and the issue of antibiotic resistance and this was reflected often in review. The review was disguised promotion. Indeed the mention of Duac and certain of its benefits appeared in a discussion of benzoyl peroxide combination therapies and selectively in the conclusion. Prescribing information should have been provided. A cost comparison of topical treatments, including Duac, appeared simply to be based on medicine acquisition cost and did not allow for varying treatment durations, indications, pack sizes and importantly, cost efficacy. This was misleading and unbalanced. The complainants alleged that reprints of the review had been used promotionally.

The Panel noted that the supplement in question had been sponsored and facilitated by Stiefel. An agency working on behalf of the company had identified experts to be part of the Acne Working Group. Invitations sent by Stiefel stated that Stiefel would like the group to develop rigorous and robust guidance, including a treatment algorithm, to help inform clinicians on the management of mild and moderate facial acne and the relative position of topical combinations vs oral antibiotics and retinoids. Stiefel had thus, at the outset, defined the scope of the Acne Working Group. The chair had been briefed by a senior brand manager. At the groups first meeting Stiefel had given a short presentation on the role for topical combination treatments and provided factual information on its products. Stiefel had reviewed the supplement before it was released and had subsequently given its representatives copies to give to GPs and had referred to the guidance in its promotional material for Duac.

The Panel considered that Stiefel was wholly responsible for the Acne Working Group and thus for any output from it. The group was formed at

Stiefel's behest and the company had defined the scope of its work in the invitation it had issued and had briefed the chairman. There was no strictly arm's length arrangement.

The Panel considered that the material at issue was not a supplement 'Provided as a service to medicine by Stiefel' as stated on the front cover, but a paid for insert reporting the outcome of a group which had been charged, *inter alia*, with informing clinicians about the relative position of topical combination products in the treatment of mild to moderate facial acne. The group concluded that combination therapies involving benzoyl peroxide might assist in patient concordance and the minimization of antibiotic resistance. The Panel did not consider that the statement 'Provided as a service to medicine by Stiefel' accurately reflected the nature of the company's involvement. A breach of the Code was ruled. It was not stated that the Acne Working Group had been formed by Stiefel. The Panel considered that the material was disguised promotion as alleged. A breach of the Code was ruled.

The Panel noted that the supplement contained a table of data headed 'Cost comparison for acne treatments'. Readers were directed to a footnote which stated that costs had been taken from MIMS January 2008. In that regard the Panel considered that the table listed acquisition costs only; there was no implication that the table detailed cost efficacy of the medicines. The Panel did not consider that the table was unbalanced or misleading as alleged. No breach of the Code was ruled.

The Panel considered that presenting the output of the Acne Working Group as an independent supplement to a journal demonstrated apparent poor knowledge of the requirements of the Code. Health professionals generally looked to medical journals as a source of independent information; where authors wrote on behalf of companies or as a result of the activities of pharmaceutical companies this must be made clear. In the Panel's view the majority of readers would have viewed the material at issue quite differently if they had known the relationship between the Acne Working Group and Stiefel. High standards had not been maintained. A breach of the Code was ruled.

A general practitioner and a pharmacist jointly complained about the promotion of Duac Once Daily Gel (clindamycin 1% and benzoyl peroxide 5%) by Stiefel Laboratories Ltd. The materials at issue were a GP leavepiece (ref DU:7076UK); a pharmacist leavepiece (ref DU:E7156UK); two journal advertisements (refs DU:E7121UK and DU:E7232UK); two abbreviated advertisements (refs DU:E7233UK and DU:E7168UK) and a GP Review, January 2008, Management of mild and moderate acne vulgaris (ref DU:E7120UK). Duac was indicated for the treatment of mild to moderate acne vulgaris, particularly inflammatory lesions.

When writing to Stiefel the Authority asked it to respond in relation to Clauses 3.2, 7.2, 7.4, 7.5, 7.7, 7.10, 9.1, 9.10 and 12.1 of the Code.

1 Provision of references

COMPLAINT

The complainants noted that whilst developing a review article on the management of acne in primary care, one of them telephoned Stiefel's medical information department on 29 May to ask for copies of references cited in the Duac promotional materials; Langner *et al*, (2007); patient preference study, data on file, Stiefel Laboratories (2001); Acne Working Group GP Review January 2008 and Langner *et al* (2008).

The company was not cooperative; its response bordered on being initially uninterested and then belligerent. The medical information person stated that she could not give an assurance that she could provide the data-on-file as it might not be available. After much insistence and reference to the Code, the complainants were finally assured that their request would be treated as urgent. Unfortunately, over two weeks later the information had not been received. This was disappointing and of concern to the complainants. In the meantime the complainants had independently sourced three references which were in the public domain.

RESPONSE

Stiefel submitted that its recollection of the telephone call differed from the complainants; principally in that it was explained that all documentation would be provided, but it might take up to 10 working days to arrive. The caller would not provide an email or telephone details and asked for the documents to be posted to a personal address.

Stiefel submitted that its records showed that only two references were requested, not three or four as suggested. These references were posted to the given address on 9 June 2009, but were returned on 22 June as 'addressee unknown'. Since the complaint had been anonymised Stiefel was unable to guarantee that the telephone call was actually the one referred to in the complaint, however, given the subject matter and timing this seemed rather likely.

PANEL RULING

The Panel noted that the complainants and respondent did not agree on what the complainants had requested. It was impossible to know what exactly transpired between the parties. Nonetheless the Panel noted the submission that references (Langner *et al* 2007 and data on file 2001) had been posted to one of the complainants on Tuesday, 9 June, seven working days after the initial request for papers. Unfortunately the house number recorded on the telephone enquiry report was wrong by one digit and thus some days later, the

package was returned to Stiefel marked 'addressee unknown'. It was unfortunate that the wrong address had been recorded however, in the Panel's view, such an error did not constitute a breach of the Code. References had been posted in a timely manner and so no breach of Clause 7.7 of the Code was ruled.

APPEAL FROM THE COMPLAINANTS

The complainants submitted that the company's response was inconsistent with the need for the medical information department to maintain high standards. It was incredible that the company cited the minutiae of its records as a reliable/flawless record of what was discussed and simultaneously expected the complainants to believe that this record of events somehow and crucially allowed the erroneous recording of key information such as the first line of the complainant's address. This called into question the veracity of the company response. The Panel seemed to suggest that as long as a company could demonstrate it sent the information requested in a timely manner it did not ultimately matter where any response was sent, even when the correct information was provided. This effectively absolved companies from the need to demonstrably maintain high standards and simply ensured that they only needed to tick the necessary boxes. This was very convenient for a company which might be unable or unwilling to respond to requests for certain information. Ultimately the ruling meant that it was for the busy health professional to be encumbered and pursue the company for undelivered information and given the ruling, it was not to say that the second time around it would be sent to the correct address … as long it was sent somewhere!!

COMMENTS FROM STIEFEL

Stiefel submitted that the call was answered by a highly experienced medical information officer. During the call the enquirer was asked if he would email the exact details of his request as she was unfamiliar with the material he was requesting, but the caller declined. The medical information officer also offered to let the caller know when he would receive the material, but he refused to provide his email and telephone details. The caller provided his name, a personal address and his Royal Pharmaceutical Society of Great Britain (RPSGB) registration number. These details were read back to him and he confirmed that they were correct. It was explained to the caller that all documentation would be provided, but because it had to be sourced via Stiefel's information services department it might take up to 10 working days to arrive. A request for the two references asked for by the caller was emailed to Stiefel's information department on the same day and the urgency of the request was also stated in this email. The references were then sent out to the address Stiefel had documented for the caller.

Stiefel regretted that the information was then sent to what turned out to be an incorrect address and that this had inconvenienced the complainant. However, Stiefel believed that it had responded in a timely and appropriate manner and tried to ensure that it had as much information as possible to ensure the request was addressed in full. Stiefel's records demonstrated its intent to fulfil the caller's request and that it was given priority. Stiefel believed that every effort was made to comply with the customer's request and the requirements of the Code and therefore it supported the Panel's ruling that it was not in breach of Clause 7.7 of the Code.

FINAL COMMENTS FROM THE COMPLAINANTS

There were no further comments from the complainants.

APPEAL BOARD RULING

The Appeal Board noted that, at the outset, the caller had been advised that it might take up to ten working days for him to receive the requested references. On the same day that it was received, the request for the papers was emailed to Stiefel's information department and marked urgent.

The references (Langner *et al* 2007 and data on file 2001) were posted to the enquirer on Tuesday 9 June, seven working days after his initial request. Unfortunately due to an error in the house number recorded on the telephone enquiry form, the package was returned to Stiefel marked 'addressee unknown'. At this point Stiefel had not been able to contact the enquirer by any other means as he had refused to provide any alternative contact details when asked by Stiefel. The Appeal Board considered that although there had been a genuine error in the recording of the house number the complainant's request had, nonetheless, been dealt with in a timely manner. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.7. The appeal on this point was thus unsuccessful.

2 Use of an acne grading chart

An acne grading chart depicting mild, moderate and severe acne appeared in the GP leavepiece.

COMPLAINT

The complainants alleged that the leaflet was inconsistent with the therapeutic indication of Duac Once Daily Gel which was to treat mild to moderate acne vulgaris, particularly inflammatory lesions. The leaflet depicted an acne grading chart which featured not only inflammatory lesions but also, non-inflammatory and nodulocystic lesions. The chart featured severe lesions and thus misleadingly implied that Duac could be used for lesions other than those that were mild to moderate.

RESPONSE

Stiefel submitted that the leavepiece clearly stated the therapeutic indication of Duac Once Daily Gel. The use of the acne grading chart was intended to provide an overview of the scale of acne disease and demonstrated where Duac Once Daily Gel could be used. Duac Once Daily Gel was written underneath the mild and moderate section with an arrow spanning the two categories. The severe acne section was separated from the mild and moderate sections. As it stood, it was clear that there were patients on the grading scale for whom Duac Once Daily Gel would not be suitable. Stiefel submitted that the chart was not misleading.

PANEL RULING

The Panel noted that page 1 of the leavepiece showed a photograph of three teenage boys and referred to 'An acne treatment for their world'. Inside the leavepiece an acne grading chart showed photographic examples of mild acne on the left-hand side of the page through to moderate and then severe acne on the right-hand side of the page. Below the pictures of mild and moderate acne was the Duac product logo and a horizontal double-headed arrow marked 'An acne treatment for their world'. The pictures of severe acne on the right-hand side of the leavepiece were slightly separate from the other pictures. The Panel noted that it was only in the prescribing information where it was explicitly stated that Duac was for mild to moderate acne.

The Panel considered that an acne grading chart showing all the grades of acne was useful so that a prescriber could tell when the condition was too severe to be treated with Duac. Nonetheless, if all grades of acne were to be shown, prescribers must be very clearly informed of when to use Duac; in that regard the Panel considered that a double-headed arrow spanning the pictures of mild to moderate acne and the statement in the prescribing information were insufficient. Some readers might assume that Duac could be used for severe acne. The Panel considered that the leavepiece was inconsistent with the particulars listed in the Duac summary of product characteristics (SPC). A breach of Clause 3.2 was ruled. The Panel further considered that the leavepiece was misleading about the product's licensed indication and in that regard did not encourage the rational use of Duac. Breaches of Clauses 7.2 and 7.10 were ruled.

3 Claim 'Duac Once Daily Gel works fast'

This claim appeared in the GP and pharmacist' leavepieces referenced to Langner *et al* (2007).

COMPLAINT

The complainants alleged that the unqualified and generalised claim that Duac worked fast was misleading, exaggerated the facts, could not be substantiated and was inconsistent with the SPC. The SPC stated that patients should be advised that in some cases 4-6 weeks of treatment might be required before the full therapeutic effect was observed. A clinical study, Langner *et al* (2007), was cited in support of this unqualified claim to suggest that the data were not only clinically significant but also statistically significant. However, the study did not substantiate the claim. The primary efficacy variable of the study was to assess the proportion of patients showing at least a 30% improvement from baseline of non-inflammatory and inflammatory lesion count at weeks 1 and 2. The secondary endpoints were the proportion of patients showing a 30% improvement or greater from baseline at weeks 4, 8 and 12 and in total lesion counts at all post-baseline assessments. The results showed that for both treatment groups, a progressive decline was observed in the number of inflammatory and non-inflammatory lesions. The improvement was, with only one exception, greater in the group treated with Duac than in the comparator group; the difference was close to/approached significance at week 1 for inflammatory lesions but was only statistically significant for inflammatory and for total lesions at week 2. With the exception of week 2, the difference in inflammatory lesion counts was not statistically significant. The unqualified use of 'fast' could imply an earlier response than supported by these data.

RESPONSE

Stiefel submitted that the claim that Duac Once Daily Gel worked fast was supported by Langner *et al* (2007). The study showed that inflammatory and total lesions were statistically significantly reduced compared with the comparator, Zineryt, by week 2, with the difference approaching significance at week 1. Zineryt, was the most widely prescribed topical product for mild to moderate acne. Stiefel understood that acne patients wanted a rapid response from their treatment and it believed that a response within two weeks qualified as fast in this therapeutic category, especially when compared with competitor products. Stiefel submitted that more recent data had been generated which demonstrated that Duac Once Daily Gel started to work within one week.

Stiefel submitted that the claim that Duac Once Daily Gel worked fast was not inconsistent with the SPC, as it was well known and accepted that the full therapeutic effect of a product would be progressive. The data showed that Duac Once Daily Gel worked within two weeks and the SPC and prescribing information confirmed that the full effect might not be seen until after 4-6 weeks of treatment. The claim did not imply complete efficacy.

PANEL RULING

The Panel noted that the study cited in support of the claim (Langner *et al* 2007) was a comparison of Duac and Zineryt in the treatment of mild to

moderate facial acne. The claim at issue, however, was not comparative and did not compare Duac's efficacy or time to onset of action with that of Zineryt.

Langner *et al* (2007) showed that from week 0 to week 1, the total number of non-inflammatory lesions in patients treated with Duac (n=73) fell from a mean of 53.4 to 41.8, similarly the mean total number of inflammatory lesions fell from 34.3 to 27.9 and the mean total number of lesions fell from 87.7 to 69.7. Over 20% of patients treated with Duac showed at least a 30% reduction in total lesion counts at week 1 and over 60% showed at least a 30% reduction in total lesion counts at week 2. The Panel considered that the claim 'Duac Once Daily Gel works fast' was not misleading or exaggerated as alleged. No breach of Clauses 7.2 and 7.10 were ruled. The claim had been substantiated and so no breach of Clause 7.4 was ruled. The Panel did not consider that the claim was inconsistent with the SPC as alleged. No breach of Clause 3.2 was ruled.

APPEAL FROM THE COMPLAINANTS

Whilst the complainants welcomed the ruling of breaches of Clauses 7.2 and 7.3 of the Code regarding the claim that Duac worked within one week (Point 8 below) they would like the Panel to qualify its ruling with regard to the claim that Duac 'works fast'. The latter claim was unqualified with regard to defining a specific time period for the term 'fast'. The substantiation for this term was pegged to 7-14 days after treatment. As such, this unqualified claim could still mislead by implying that Duac was effective within seven days. The complainants alleged that appropriate qualification of the claim was necessary without which it was in breach of the Code.

COMMENTS FROM STIEFEL

Stiefel submitted that the items in question were clear in that Duac was indicated for the treatment of mild to moderate acne. The additional information relating to the speed of action of Duac was substantiated by the clinical data and was not inconsistent with the terms of its marketing authorization. The SPC stated that 'Patients should be advised that, in some cases, 4-6 weeks of treatment may be required before the full therapeutic effect is observed', but this was not in contradiction with the fact that approximately 20% of patients experienced a 30% improvement within a week. Therefore, Stiefel supported the Panel's ruling and denied a breach of Clause 3.2 of the Code.

Stiefel submitted that health professionals and chronic acne sufferers were aware that most treatments took several weeks to have a noticeable effect and therefore any treatment that worked within a week or two was generally regarded as fast-acting. Stiefel noted that Luckey *et al* (2007) concluded that Dapsone gel acted fast in acne vulgaris because a significant effect was observed at week 4.

Stiefel submitted that Langer *et al* (2007), a comparison between Duac and Zineryt, and Langer *et al* (2008), a comparison between Duac and Adapalene, showed that Duac worked within a week and acted faster than either comparator. To date, Stiefel was not aware of any published head-to-head comparisons which showed any alternative topical mild to moderate acne treatment had a faster onset of action than Duac Once Daily Gel.

Given that physicians understood that a 'fast' treatment for acne worked within 4 weeks, and the enclosed Duac information, Stiefel submitted that its statement, based on an even faster effect, was accurate, fair and capable of substantiation and promoted the rational use of its medicine. Therefore, Stiefel supported the Panel's ruling and continued to deny a breach of Clauses 7.2, 7.4 and 7.10 of the Code.

FINAL COMMENTS FROM THE COMPLAINANTS

The complainants reiterated that they welcomed the ruling regarding the claim that Duac worked within one week particularly as it was inconsistent with the Duac SPC and that approximately 20% of patients on Duac experiencing any improvement in any time period hardly constituted the balance of evidence or probability of what might reasonably be expected by the other 80%!

The complainants wanted the Panel to qualify its ruling with regard to the claim that Duac worked fast for the reasons stated above.

APPEAL BOARD RULING

The Appeal Board noted that the study cited in support of the claim (Langner *et al* 2007) showed that from week 0 to week 1, the total number of non-inflammatory lesions in patients treated with Duac (n=73) fell from a mean of 53.4 to 41.8, similarly the mean total number of inflammatory lesions fell from 34.3 to 27.9 and the mean total number of lesions fell from 87.7 to 69.7. Over 20% of patients treated with Duac showed at least a 30% reduction in total lesion counts at week 1 and over 60% showed at least a 30% reduction in total lesion counts at week 2.

The Appeal Board noted that the audience (GPs and pharmacists) would be familiar with the treatment of acne, and would consider that a topical treatment which showed results after one to two weeks would be considered as acting 'fast'. The Appeal Board noted that Luckey *et al* concluded that an acne treatment acted fast because a significant effect was observed at week 4. Teenagers would want to know that they could expect to see a positive response to therapy after a week or so. In this regard the Appeal Board noted that it would take much longer before oral therapies were seen to have an effect. The Appeal Board did not consider that health professionals would be misled as to assume that the claim implied that the full therapeutic effect of Duac would be achieved 'fast'.

The Appeal Board considered that the claim 'Duac Once Daily Gel works fast' was not misleading or exaggerated as alleged, and it thus upheld the Panel's ruling of no breach of Clauses 7.2 and 7.10. The claim had been substantiated and so the Panel's ruling of no breach of Clause 7.4 was also upheld. The Appeal Board did not consider that the claim was inconsistent with the SPC as alleged and upheld the Panel's ruling of no breach of Clause 3.2. The appeal on this point was thus unsuccessful.

4 Claim that Duac is 'cosmetically acceptable'

This claim appeared in the GP and pharmacist leavepieces and was referenced to data on file (2001).

COMPLAINT

The complainants alleged that the data on file cited to support the claim of cosmetic acceptability was not in the public domain and had not been provided as per their request. However, it was clearly not up-to-date and one could reasonably surmise that the data was unlikely to substantiate the claims of cosmetic acceptability with particular reference to the modern contemporary teenagers depicted in the leaflets. It was also very likely that today's teenagers had a very different perspective on what was cosmetically acceptable compared with the prevalent view of their peers in 2001. The claim of cosmetic acceptability focused entirely on the teenagers' need to look good and not silly. However, the latter ignored the occurrence of important side-effects which commonly included erythema, peeling, dryness, burning and pruritis which also needed to be balanced whilst pursuing aesthetics. This was not responsible promotion. The emphasis on cosmetic acceptability, particularly with regard to the face as opposed to other equally important parts of the body was not only inconsistent with the SPC but also tantamount to suggesting that this product was to be used as a cosmetic.

RESPONSE

Stiefel submitted that the data on file referred to was posted to the complainants on 9 June 2009 but returned on 22 June as 'addressee unknown'. There was no substantiation to the claim that this data was no longer relevant to teenagers today, nor was it known on what basis the complainants could determine that the data was unlikely to substantiate the claims made, as the data on file had not been reviewed by them.

In the data on file Stiefel believed that the parameters assessed (smell, colour, feel of the product etc) were as relevant today as they were in 2001 when the study was conducted. Stiefel submitted that there was no suggestion that Duac Once Daily Gel could be used as a cosmetic and it did not believe there was any way in which this inference could be made. The term 'cosmetic acceptability' was well known and understood to mean how acceptable the physical characteristics of the product were to the patient.

In response to a request for further information, Stiefel explained that the Clindoxyl formulation used in the sensory comparison, which was marketed in Canada and the US, contained methyl parabens as a preservative, whilst the Duac formulation marketed in the EU did not. There was also a difference in the grade of carbomer used in order to meet the requirements of the European Pharmacopoeia. In all other respects the formulations were the same and there were no differences that would affect the aesthetic and sensory qualities of the product.

PANEL RULING

The Panel noted that the data on file cited in support of the claim was a study which had compared the consumer acceptability of Clindoxyl Gel and Benzamycin gel on the basis of immediate perception of aesthetic attributes and after one week's use. Patients (n=51) were asked to rate the smell of the products, their colour and their feel on the skin in terms of greasiness, granularity, spreadability, and whether they left a residue/film. Patients were also asked if they had experienced stinging and to rate the ease of applying make-up after applying the product to their skin. Subjects preferred Clindoxyl Gel over Benzamycin on virtually each attribute and on an overall basis.

The Panel noted that the complainants had not seen the data on file and had complained that, *inter alia*, results from 2001 would not be relevant to teenagers in 2009. No rationale was provided for this argument. The Panel did not consider that the claim was misleading in that regard. No breach of Clause 7.2 was ruled. The Panel considered that on the basis of the results of the consumer acceptability study, it was not unreasonable to claim that Duac Once Daily Gel was cosmetically acceptable. The claim was not misleading as alleged and had been substantiated. No breach of Clauses 7.2 and 7.4 were ruled. The Panel did not consider that the claim was tantamount to suggesting that the product was a cosmetic. In that regard the claim encouraged the rational use of the medicine. No breach of Clause 7.10 was ruled.

During the consideration of this point, the Panel noted that the complainants had referred to the side effects of Duac Once Daily Gel ie erythema, peeling, dryness, burning and pruritis. In the Panel's view the cosmetic acceptability of a product was different to its side-effect profile. In each leavepiece, under the claim of cosmetic acceptability, was the stabpoint 'non-drying'. The SPC, however, in Section 4.8, Undesirable effects, listed dryness as a very common (> 1/10) side effect. The Panel was thus concerned that the claim 'non-drying' was inconsistent with the particulars listed in the SPC and requested that Stiefel be advised of its views in that regard.

5 Claim 'Duac Once Daily Gel gets on with teenagers'

This claim appeared in the GP leavepiece.

COMPLAINT

The complainants noted that the leavepiece claimed that Duac Gel got on with teenagers. This was a claim of efficacy in this particular patient group which appeared to be unsubstantiated. Indeed the cited reference, Langer *et al* (2007), did not substantiate the claim as the mean age of the subjects was 21.2 years in the Duac arm of the study.

RESPONSE

Stiefel submitted that Duac Once Daily Gel was licensed for the treatment of mild to moderate acne vulgaris in all age groups (except children under 12 years of age). The claim that Duac Once Daily Gel 'gets on' with teenagers was intended to reflect the characteristics of the product that would make its use as convenient as possible to teenagers. These characteristics were listed below the statement, giving it clear context.

PANEL RULING

The Panel noted that Langner *et al* (2007) set out to treat patients aged 12-39 years who had mild to moderate facial acne. Patients in the Duac group were aged 12-38 and had a mean age of 21.2 years. There was no data before the Panel which suggested that the efficacy of Duac differed according to the age of the patient.

In the GP leavepiece the headline 'Duac Once Daily Gel gets on with teenagers' was followed by a number of claims regarding the ease of use/acceptability of Duac eg once daily application, odour free etc. The Panel further noted, from point 3 above, that the majority of patients had at least a 30% decrease in total lesion count at two weeks. In the Panel's view this onset of action time would encourage compliance in a group where compliance was likely to be difficult.

On balance the Panel considered that the claim 'Duac Once Daily Gel gets on with teenagers' had been substantiated. No breach of Clause 7.4 was ruled.

6 Claims 'Teenagers are "busy" Duac is a once daily gel' and 'can be worn under make-up'

The 'busy' claims appeared in the GP and pharmacists' leavepieces. One advertisement (ref DU: E7232UK) stated 'Once a day is good, because they're, like, so busy'. The advertisement and the pharmacist leavepiece also featured the 'make-up' claim.

COMPLAINT

The complainants alleged that the issue of convenience was overstated particularly given that the SPC clearly suggested certain restrictions which might be important to teenagers with regard to the administration of Duac. The SPC stated that the gel should be applied once daily in the evening to affected areas after the skin had been thoroughly washed, rinsed with warm water and gently patted dry. The complainants were not sure that this strict regimen was consistent with the ease of use implied by the unqualified once daily application claim in support of the use of Duac for teenagers who were impatient and busy. Also the claim that Duac could be used under make-up might be relevant to young teenagers, however in the early phase of the treatment of moderate acne it was generally accepted that cosmetics should be avoided in order to detect side effects and indeed some products should be avoided all together. The focus on an early response aligned with less than helpful and unqualified generalisations regarding the use of cosmetics was misleading and irresponsible.

RESPONSE

Stiefel submitted that a basic hygiene regimen was a standard aspect of topical acne treatments. It was unlikely that washing and drying the skin before use would be considered a 'strict regimen' by patients. The claim of a once daily application for Duac Once Daily Gel was qualified by the SPC which stated that Duac Once Daily Gel should be applied once per day. This was in line with the clinical evaluations conducted prior to product registration. A once daily application was preferential to a twice daily application, as evidenced by data on file.

Stiefel submitted that Duac Once Daily Gel could be worn under make-up and it was generally accepted that people would wish to continue to use make-up during treatment. Additionally, there were many make-up products available to camouflage acne. It was, of course, at the discretion of the prescriber to suggest whether make-up was worn; the claim was simply that Duac Once Daily Gel could be worn under make-up.

PANEL RULING

The Panel noted that Duac should be applied once daily in the evening, to affected areas after the skin had been thoroughly washed, rinsed with warm water and gently patted dry. The Panel did not consider that this was a strict regime as alleged or that it imposed restrictions on 'busy' teenagers. No breach of Clause 7.2 was ruled.

With regard to wearing make-up, the Panel noted that the Duac SPC stated in Section 4.5 (interaction with other medicinal products and other forms of interaction) that, *inter alia*, cosmetics that had a strong drying effect, and products with high concentrations of alcohol and/or astringents, should

be used with caution as a cumulative, irritant effect might occur. There was no clinical data before the Panel to support the concomitant use of make-up. The Panel considered that the claim 'can be worn under make-up' did not reflect the evidence and was misleading in that regard. A breach of Clause 7.2 was ruled.

7 Claim 'No need to keep it in the fridge'

This claim appeared in the GP leavepiece.

COMPLAINT

The complainants noted that the leavepiece was aimed at health professionals and alleged that the claim that there was no need to keep Duac in the fridge was incomplete and therefore misleading. The storage of conditions prior to dispensing [store in a refrigerator at 2-8°C] were important and had been omitted; this information was relevant to both pharmacists and dispensing GPs.

RESPONSE

Stiefel noted that the claim 'No need to keep it in the fridge' was listed within a section of claims regarding the suitability of Duac Once Daily Gel to patients, in particular teenagers. It was clear that the statement referred to use by patients.

Stiefel submitted that the leavepiece in question was designed specifically for non-dispensing prescribers. A separate leavepiece for dispensing prescribers and pharmacists (DU:E7156UK) clearly stated the storage conditions before and after dispensing.

PANEL RULING

The Panel noted that the leavepiece at issue (ref DU:7076UK) was specifically for non-dispensing prescribers ie those who would not need to store Duac prior to dispensing. The claim 'No need to keep it in the fridge' appeared as the fourth bullet point on a page headed 'Duac Once Daily Gel gets on with teenagers'. In the context in which it appeared the Panel considered that the claim was about the patient's use of Duac, not the dispenser's storage of the product. In that regard the Panel did not consider that the claim was misleading as alleged and so no breach of Clause 7.2 was ruled.

8 Claim 'Duac … starts working within a week'

This claim appeared on an advertisement (ref DU:E7233UK) and an abbreviated advertisement (ref DU:E7121UK). The claims were unreferenced. Both advertisements showed a picture of a young man sitting in a doctor's waiting room with his head down and hidden in the hood of his jacket.

COMPLAINT

The complainants alleged that the claim that Duac Once Daily Gel started working within a week was misleading and unsubstantiated. Langner *et al* (2008) was cited in support of this claim. This was a small, single-blind study which did not represent the balance of evidence in respect of the speed of onset of action of Duac. The primary efficacy variable was the absolute values and the percentage change from baseline in inflammatory lesion counts at week 2. There was no mention of this in the advertisements. The claim misleadingly only referred to data relating to the secondary endpoints which were the absolute values and the percentage change from baseline in inflammatory lesion counts at weeks 1, 4, 8 and 12 and in non-inflammatory and total lesion counts at all post-baseline assessments. The results indicated that the difference between groups for the percentage change from baseline was statistically significant, but only from/at week 1 onwards. This latter was clearly not consistent with the wording 'within a week'. Specifically the comparison was with Differin Gel and any claim of fast onset of action should be qualified to clarify the comparison as it might not be relevant when compared with other topical treatments.

The complainants alleged that the advertisement also appeared to imply that the speed of onset of action and effectiveness of Duac somehow improved teenagers' confidence with particular reference to facial acne rather than lesions on other parts of the body to such an extent that patients could stop hiding under their hoodies within one week. The latter was clearly a generalisation which was inconsistent with the SPC. The latter did not make any specific recommendations or indicate that Duac was specifically indicated and effective in the management of facial acne over and above lesions on other parts of the body. After all the confidence of teenagers who enjoyed swimming, for example, would not necessarily be enhanced if the rapid effectiveness of Duac did not extend to the legs and arms. The promotion of this aspect of the benefits of Duac was inappropriately exaggerated and distorted the premise for rational prescribing.

RESPONSE

Stiefel submitted that Langner *et al* (2008) stated that Duac showed an earlier onset of action with a faster significant reduction in inflammatory and total lesion counts than Differin Gel. A between-group comparison of the percentage change from baseline showed that Duac was statistically significantly superior to Differin Gel from week 1 onwards both for inflammatory lesions ($p \leq 0.001$) and for total lesions ($p \leq 0.004$). The authors concluded that Duac had a significantly earlier onset of action, was significantly more effective against inflamed and total lesions and was better tolerated, which should improve patient compliance.

Langner *et al* (2008) also assessed clinical acne grade and demonstrated that 'acne grade decreased in both treatment groups; however, this decrease was more significant with Duac, with statistical

significance (p = 0.013) being achieved as early as week 1'. Given that a statistically significant reduction in clinical acne grade was seen by week 1 with Duac Once Daily Gel, Stiefel submitted that it was appropriate to claim a fast onset of action.

Stiefel submitted that it did not know of any published head-to-head comparisons which showed that any alternative topical mild to moderate acne treatment had a faster onset of action than Duac Once Daily Gel.

The advertisements did not imply efficacy in any one part of the body over another and Stiefel could not understand how the advertisement could be inconsistent with the SPC in this regard.

PANEL RULING

The Panel considered data to substantiate the claim that Duac 'starts working within a week' would have to show that the product was effective in less than seven days. The Panel had no such data before it. Both Langner *et al* (2007) and Langner *et al* (2008) reported efficacy at week one but not before then. The Panel thus considered that the claim was misleading and had not been substantiated; breaches of Clauses 7.2 and 7.4 were ruled. The Panel considered that the claim was about Duac alone; it was not a comparison with Differin Gel or any other product. In that regard the Panel did not consider that the claim was a misleading comparison as alleged and no breach of Clause 7.3 was ruled.

The Panel did not consider that the advertisements implied that Duac was particularly effective for facial acne as opposed to acne on any other part of the body. In the Panel's view the advertisements depicted a typical acne patient. The Panel did not consider that the advertisements inappropriately exaggerated or distorted the premise of rational prescribing as alleged. No breach of Clause 7.10 was ruled.

9 Acne Working Group GP Review January 2008

This review was cited in support of general claims about acne in the pharmacist leavepiece.

COMPLAINT

The complainants stated that it was evident that the Acne Working Group was convened at the behest of Stiefel which was close to the discussions and in control of the outputs from this working group. The cover of the article looked like the independent parent journal, GP, and this in conjunction with the statement that the review was provided as a service to medicine by Stiefel misled the reader because it implied that it was not promotional. Promotional claims for Duac were principally about the importance of benzoyl peroxide and the issue of antibiotic resistance and this was reflected often in the article. The review was disguised promotion for Duac. Indeed the mention of Duac and certain of its benefits appeared in a discussion of benzoyl peroxide combination therapies and selectively in the conclusion. Given the latter and the clearly promotional nature of the article, prescribing information should have been provided. The article also invited a cost comparison of topical treatments including Duac. Unfortunately it appeared simply to be based on medicine acquisition cost and did not allow for varying treatment durations, indications, pack sizes and importantly, cost efficacy. This was misleading and unbalanced. The complainants also alleged that reprints of the review had been used promotionally.

RESPONSE

Stiefel submitted that the reference code was to allow easy identification of the piece in circumstances such as these. It did not mean that the piece had undergone full editorial review by Stiefel nor did it mean that it was a promotional item.

Stiefel had appointed an external, independent medical education company to organise a working group to produce a primary care treatment algorithm for acne, as there was no other relevant guidance available. The review also looked at the psychological impact of acne. Stiefel did not control the output from this group nor did it have editorial control over the article. Stiefel considered that the article was balanced and fair.

Stiefel submitted that the article provided a balanced overview of acne management and recommended benzoyl peroxide or topical retinoid as first line treatment in mild acne and a combination of either an antibiotic or retinoid with benzoyl peroxide for moderate acne. Products were not mentioned by brand name in the article.

The article referred to antibiotic resistance and the use of benzoyl peroxide to prevent, eliminate or reduce the generation of resistant bacteria. This was an important topic in the treatment of acne with topical antibiotics and it was therefore appropriate to the article. Although the article mentioned the use of clindamycin plus benzoyl peroxide combinations, it also discussed the use of benzoyl peroxide monotherapy and the use of separate benzoyl peroxide and antibiotic products.

Stiefel submitted that the article provided a cost comparison based on acquisition costs as per MIMS. Duac Once Daily Gel was mentioned, along with all other acne products listed. It was difficult, and seemed to require a biased point of view, to see this as a cost comparison of Duac Once Daily Gel against other products, rather than an overview of all products. Stiefel noted that a direct comparison of unit acquisition costs was not favourable for Duac Once Daily Gel.

In conclusion, Stiefel submitted that none of the complainant's comments were justified, it had acted

in accordance with the Code and maintained a high standard throughout.

In response to a request for further information Stiefel explained that the review was a Stiefel sponsored initiative, to address the need for guidance in primary care with regard to the management of acne as there was no other relevant guidance available. The review would also look at the psychological impact on acne sufferers. At no point did Stiefel control the output from the group or have editorial control over the article.

The opinions reflected those of the authors. However, Stiefel acknowledged that, by sponsoring and facilitating the review, the acne working group was not fully independent, and so in the original publication of the review and the subsequent reprints, Stiefel's sponsorship was clearly highlighted.

Stiefel explained that potential members of the Acute Working Group had been proposed by the medical communications agency appointed to co-ordinate the work. Stiefel had agreed to the list of potential members but had not suggested who any of the working group should be.

What was required of the members was clearly outlined in the invitation from Stiefel ie:

- to join the Acne Working Group to develop rigorous and robust guidance for the treatment of mild and moderate facial acne, including a treatment algorithm and the relative position of topical combinations vs oral antibiotics and retinoids
- to attend two meetings in 2007 in central London
- to receive an honorarium plus reasonable travel expenses
- to complete an acceptance and availability form and return to the agency.

The chair was briefed by a senior brand manager with regard to the requirement as the chair of the group. This meeting was followed up with a confirmation letter (a copy was provided).

The first of the two meetings took place in September 2007 in London. In attendance were the Acne Working Group, a senior manager from Stiefel and a medical writer, organised by the medical communications agency to take notes and prepare the manuscript for circulation after the two meetings. There were no other attendees from Stiefel or the agency.

The second meeting took place on Thursday, 22 November 2007 in London from 10am - 4pm. The attendees at this meeting were the Acne Working Group and the medical writer. There were no attendees from Stiefel or the agency. Again the group had a working lunch and details of refreshments could be provided.

An initial draft of the content of the supplement at issue was developed from the outcome of the two meetings and this was circulated to the Acne Working Group for comment. This process was repeated until the group agreed on the content.

The final version was put through the Stiefel approval system to proof read for accuracy and to ensure that no comments were misleading, before being released to GP for publication as a supplement with the statement 'Provided as a service to medicine by Stiefel' on the front page.

Stiefel noted that none of the Acne Working Group were involved in any of its advisory boards. Two members had been involved in research projects over a number of years. No other member of the group was involved in any other paid projects with Stiefel.

Stiefel submitted that it did not influence the scope and content of the GP review in any way and had no control over the output or the conclusions of the publication. Its only involvement was in the first meeting, in September 2007, where a senior manger attended to meet and greet the experts and provide factual information on Stiefel products.

Stiefel submitted that the supplement was produced as an independent review conducted by experts. Stiefel representatives were given reprints of the supplement to give to GPs and subsequent promotional materials referred to the guidance.

Stiefel noted that the guidance clearly stated on the front page 'Provided as a service to medicine by Stiefel' with the Stiefel logo next to it.

In conclusion, Stiefel considered that it had acted in accordance with the Code with regards to its involvement in the Acne Working Group GP Review and in the way that the ensuing documents had been used in subsequent promotional activities. The company believed that by including its logo in bold at the top of the document with the statement 'Provided as service to medicine by Stiefel', the declaration of sponsorship was sufficiently prominent to ensure that readers were aware of it at the outset, thereby complying with Clauses 9.10 and 12.1 of the Code.

PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favorable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company

and no use by the company of the material for promotional purposes.

The supplement in question had been sponsored and facilitated by Stiefel. A medical communications agency working on behalf of the company had identified experts to be part of the Acne Working Group. Invitations to be part of the group had been sent by Stiefel. The invitations had stated that Stiefel would like the group to develop rigorous and robust guidance, including a treatment algorithm, to help inform clinicians on the management of mild and moderate facial acne and the relative position of topical combinations vs oral antibiotics and retinoids. Stiefel had thus, at the outset, defined the scope of the Acne Working Group. The chair had been briefed by a senior brand manager. At the first meeting of the working group Stiefel had given a short presentation on the role for topical combination treatments. Stiefel had submitted that its senior manager had provided factual information on its products at the meeting. Stiefel had reviewed the supplement before it was released to GP. Stiefel had subsequently given copies of the supplement to its representatives to give to GPs and had referred to the guidance in its promotional material for Duac.

The Panel considered that Stiefel was wholly responsible for the Acne Working Group and thus for any output from it. The group was formed at Stiefel's behest and the company had defined the scope of its work in the invitation it had issued and had briefed the chairman. There was no strictly arm's length arrangement.

The Panel considered that the material at issue was not a supplement 'Provided as a service to medicine by Stiefel' as stated on the front cover, but a paid for insert reporting the outcome of a group which had been charged, *inter alia*, with informing clinicians about the relative position of topical combination products in the treatment of mild to moderate facial acne. The group concluded that combination therapies involving benzoyl peroxide might assist in patient concordance and the minimization of antibiotic resistance. The Panel did not consider that the statement 'Provided as a service to medicine by Stiefel' accurately reflected the nature of the company's involvement. A breach of Clause 9.10 was ruled. It was not stated that the Acne Working Group had been formed by Stiefel. The Panel considered that the material was disguised promotion as alleged. A breach of Clause 12.1 was ruled.

The Panel noted that the supplement contained a table of data headed 'Cost comparison for acne treatments'. Readers were directed to a footnote which stated that costs had been taken from MIMS January 2008. In that regard the Panel considered that the table listed acquisition costs only; there was no implication that the table detailed cost efficacy of the medicines. The Panel did not consider that the table was unbalanced or misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel considered that presenting the output of the Acne Working Group as an independent supplement to a journal demonstrated apparent poor knowledge of the requirements of the Code. Health professionals generally looked to medical journals as a source of independent information; where authors wrote on behalf of companies or as a result of the activities of pharmaceutical companies this must be made clear. In the Panel's view the majority of readers would have viewed the material at issue quite differently if they had known the relationship between the Acne Working Group and Stiefel. High standards had not been maintained. A breach of Clause 9.1 was ruled.

During the consideration of this matter the Panel was concerned to note that sponsored journal supplements which had similarly been ruled in breach of the Code because they were considered to be disguised promotion had also been ruled in breach of Clause 2. The Panel could not consider such a ruling in this case because the complainants had not explicitly or implicitly alleged that the supplement reduced confidence in or brought discredit upon the industry and so Stiefel had not been asked to consider the requirements of Clause 2. Nonetheless, the Panel requested that Stiefel be advised of its concerns in this regard.

Complaint received **17 June 2009**

Case completed **17 September 2009**

CASE AUTH/2245/6/09

PRIMARY CARE TRUST PRESCRIBING SUPPORT UNIT v LUNDBECK

Cipralex letter

A primary care trust (PCT) prescribing support unit alleged that a Cipralex (escitalopram) letter sent to a hospital physician by Lundbeck selectively quoted the advice issued in the PCT's prescribing and dispensing newsletter and presented a more positive view of escitalopram than the newsletter conveyed.

The PCT newsletter stated: 'Escitalopram has not been accepted as a formulary drug. However it is recognised that there may be infrequent occasions when it will be initiated by specialists for use in major depressive disorder (eg patients referred for specialist treatment and who have previously tried 3 other antidepressants) or in generalised anxiety disorder.'

The letter from Lundbeck stated: 'As you may be aware Cipralex (escitalopram) was recently reviewed for the [named] Formulary. It was recognised that there will be occasions when Cipralex will be initiated by specialists for use in the treatment of Major Depressive Disorder or Generalised Anxiety Disorder.'

The detailed response from Lundbeck is given below.

The Panel noted that although the letter in question stated that Cipralex had recently been reviewed for the local formulary it did not state that it had not been accepted as a formulary medicine. In the Panel's view, failure to state the formulary status might imply that the medicine had been approved for use. The letter further stated that it had been recognised that there would be occasions when Cipralex would be initiated by specialists for use in the treatment of major depressive disorder or generalised anxiety disorder. According to the PCT newsletter the local formulary committee, however, had considered that use of Cipralex would be infrequent ie when it was initiated by specialists for use in major depressive disorder (eg in patients referred for specialist treatment and who had previously tried three other antidepressants) or in generalised anxiety disorder.

The Panel considered that the brief statement in the letter omitted important details about the outcome of the local formulary review as reported in the PCT newsletter. In that regard the statement was not a complete or accurate reflection of the review and was thus misleading and could not be substantiated. High standards had not been maintained. Breaches were ruled.

A primary care trust (PCT) prescribing support unit complained about a Cipralex (escitalopram) letter (ref 0409/ESC/342/905) sent to a hospital physician by Lundbeck Ltd.

COMPLAINT

The complainant stated that the local PCT prescribing and dispensing newsletter, distributed in April 2009, published the advice given by the PCT's prescribing committee.

The wording for the use of escitalopram should be compared with the letter sent by Lundbeck in June. This had been distributed locally, though the complainant did not know to whom.

The complainant strongly argued that there had been selective quotation of the advice issued in the PCT's newsletter and that the Lundbeck wording presented a more positive view of escitalopram than the newsletter conveyed.

The PCT newsletter stated: 'Escitalopram has not been accepted as a formulary drug. However it is recognised that there may be infrequent occasions when it will be initiated by specialists for use in major depressive disorder (eg patients referred for specialist treatment and who have previously tried 3 other antidepressants) or in generalised anxiety disorder.'

The letter from Lundbeck stated: 'As you may be aware Cipralex (escitalopram) was recently reviewed for the [named] formulary. It was recognised that there will be occasions when Cipralex will be initiated by specialists for use in the treatment of Major Depressive Disorder or Generalised Anxiety Disorder.'

When writing to Lundbeck, the Authority asked it to respond in relation to Clauses 2, 7.2, 7.4 and 9.1 of the Code.

RESPONSE

Lundbeck stated that the letter (sent by one of its representatives) was intended to make clinicians aware of the current licensed indications for Cipralex, according to its marketing authorization, and the existing national guidance relating to Cipralex.

The opening sentence referred to the current position of Cipralex in the PCT. Here the letter acknowledged that there would be occasions where Cipralex might be prescribed by clinicians.

Lundbeck did not specify that these occasions 'may be infrequent', since it believed that the term 'may be infrequent' was imprecise and vague and did not specify exact pre-conditions where Cipralex should and should not be prescribed, and was only accompanied by an example ie in major depressive disorder (eg patients referred for specialist treatment and who had previously tried three other antidepressants) or in generalised anxiety disorder. Lundbeck therefore did not agree that a more positive view of Cipralex was conveyed in its letter, as alleged, since the original wording was itself non-specific. Lundbeck considered that to quote this imprecise advice would be to risk inappropriate prescribing, and it was better only to mention the advice with the expectation that the clinician would have easy access to the PCT advice.

Before sending the letter to local clinicians, Lundbeck worked with a senior clinician in the PCT who agreed that the wording of the letter was appropriate. Based on that clinician's insight, Lundbeck's view was that all practising clinicians would know about the advice on the prescribing of Cipralex from their own prescribing committee, and that it was neither Lundbeck's responsibility nor the intention of the letter to reiterate, or to misrepresent that advice. The sole intention of the letter was to state clearly how Cipralex could be appropriately prescribed, according to its summary of product characteristics and marketing authorization.

The letter did not claim that Cipralex was on the local formulary.

In summary, although Lundbeck did not intend to mislead clinicians or misrepresent the PCT, it nevertheless regretted any confusion which might have been inadvertently caused by its letter. Lundbeck's genuine aim was to draw the attention of the local clinicians to the current range of licensed indications for Cipralex, and the current national guidance to add support to the advice of the local formulary committee.

PANEL RULING

The Panel noted that although the letter in question stated that Cipralex had recently been reviewed for the local formulary it did not state that Cipralex had not been accepted as a formulary medicine. In the Panel's view, failure to state the formulary status might be seen as implying that the medicine had been approved for use. The letter further stated that it had been recognised that there would be occasions when Cipralex would be initiated by specialists for use in the treatment of major depressive disorder or generalised anxiety disorder. According to the PCT newsletter the formulary committee, however, had considered that use of Cipralex would be infrequent ie when it was initiated by specialists for use in major depressive disorder (eg in patients referred for specialist treatment and who had previously tried three other antidepressants) or in generalised anxiety disorder.

The Panel noted that it was extremely important that if pharmaceutical companies reported the views of third parties such views were reported with complete accuracy, regardless of any opinions the company might have as to the wording used by the third party. The Panel further noted that a senior clinician in the PCT had agreed that the wording of the letter was appropriate. Pharmaceutical companies, however, were wholly responsible for ensuring that their materials complied with the Code. Responsibility in that regard could not be delegated to a third party.

The Panel considered that the brief statement in the letter omitted important details about the outcome of the local formulary review of Cipralex as reported in the PCT newsletter. In that regard the statement was not a complete or accurate reflection of the review and was thus misleading. A breach of Clause 7.2 was ruled. The statement regarding the outcome of the review could not be substantiated. A breach of Clause 7.4 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted its rulings above but did not consider that the matter was such that it had brought discredit upon, or reduced confidence in, the industry. A ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. No breach of that clause was ruled.

Complaint received **26 June 20009**

Case completed **3 August 2009**

CASE AUTH/2246/7/09

ROCHE/DIRECTOR v NOVARTIS

Zometa leavepiece

Roche complained about a leavepiece for Zometa (intravenous (iv) zoledronic acid) issued by Novartis. Zometa was indicated, *inter alia*, for the prevention of skeletal related events (SREs) in patients with advanced malignancies involving bone. The leavepiece was about metastatic breast cancer.

As Roche had alleged a breach of undertaking this aspect of the complaint was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

The detailed response from Novartis to each allegation is given below.

Roche alleged that the strapline, 'Protects them to the bone', directly and indirectly implied that Zometa prevented bone metastases from occurring in the first place, rather than preventing SREs, such as fractures, in breast cancer patients already diagnosed with advanced malignancies involving bone. Roche alleged that the strapline was all-embracing, ambiguous and incapable of substantiation.

Further, Roche alleged that the strapline could be seen as a 'teaser' to elicit interest in the expected licence for Zometa as adjuvant therapy to prevent bone metastases, which the European Medicines Evaluation Agency (EMEA) was currently considering. Study data supporting this application had been presented to several major oncology congresses and were therefore familiar to many of the leavepiece's audience. This constituted promotion of a medicine in an area where it did not have a marketing authorization. Moreover, the strapline failed to maintain high standards and brought discredit upon and reduced confidence in the industry in breach of Clause 2.

The Panel noted that the front page of the leavepiece was headed 'Fight skeletal destruction with Zometa'. Attached to a stylised picture of a hip joint with a bone metastases and apparent radiating fractures was the claim 'Patients with metastatic breast cancer lead a fragile existence Handle with Zometa'. The product logo and strapline at issue, 'Protects them to the bone' appeared in the bottom right hand corner.

The Panel noted that Zometa was currently indicated, *inter alia*, to prevent SREs in patients with advanced malignancies involving bone. The Panel noted the target audience for the leavepiece but nonetheless considered that the strapline was ambiguous. Some readers might consider that it meant that Zometa could be used to protect bone from metastases and this was not so. Some readers might be familiar with reports of the antimetastatic activity of zoledronic acid (Gnant *et al* 2008). Overall the Panel considered that the meaning of the strapline was opaque such that it was inconsistent with the SPC and a breach of the Code was ruled. This ruling was upheld upon appeal by Novartis. The Panel did not consider that the strapline amounted to promotion prior to the grant of the marketing authorization and no breach of the Code was ruled. The promotion of an unlicensed indication was prohibited by the Code and thus covered by the Panel's ruling above. The strapline was misleading and not capable of substantiation and as a result did not encourage the rational use of the medicine. Breaches of the Code were ruled which were upheld on appeal by Novartis. The strapline was not a teaser as the medicine was available and information about it had been given. Although the Panel considered that overall high standards had not been maintained and a breach of the Code was ruled this was overturned on appeal by Novartis. The Panel considered that the strapline in itself had not failed to recognise the special nature of medicines and the professional standing of the audience. Nor was it likely to cause offence. No breach of the Code was ruled. Clause 2 was used as a sign of particular censure and reserved for such use. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2; no breach of the Code was thus ruled.

The claim 'Zometa reduces the risk of SREs' appeared as the heading to page two of the leavepiece which depicted a Forest plot headed 'Overall risk of skeletal events in advanced cancer by individual drug at recommended dosing'. The claim was referenced to Pavlakis *et al* (2005) a Cochrane Review on Bisphosphonates for Breast Cancer. The Forest plot included risk reduction figures and p values from a number of studies for Zometa, iv pamidronate, iv ibandronate, oral ibandronate and oral clodronate vs placebo or no treatment. A footnote below the Forest plot stated that it was adapted from Pavlakis *et al* and that 'Original trials may have had different endpoints'.

Roche was concerned about the context in which the claim 'Zometa reduces the risk of SREs' was used. The Zometa trial shown in the Forest plot included only 228 Japanese women for whom no other bisphosphonates were available at that time. As this population was not comparable with that in the UK why should it alone be used to promote a UK medicine when other Level 1 evidence in a European population was available? This

constituted cherry picking of data.

Roche alleged that if, as submitted by Novartis, the heading was clearly supported by line 1 in the Forest plot, then only the top row of the Forest plot, which related to Zometa (Kohno *et al* 2005) needed to be included. Pavlakis *et al* was a meta-analysis of bisphosphonates as a class and was not designed to draw comparisons between the various bisphosphonates. Roche alleged the overall impression created by the page implied a comparison between Zometa and other bisphosphonates and a claim for superior efficacy which the authors had not intended. Therefore, 'Zometa reduces the risk of SREs' in the context in which it was used was an unbalanced reflection of the data presented, misled the reader and was incapable of substantiation by Pavlakis *et al* to which it was referenced. The page did not include data solely on Zometa and the title did not make it clear that the graph related to bisphosphonates as a whole.

The Panel considered that the heading 'Zometa reduces the risk of SREs' in itself was not unreasonable. The allegations related to the page as a whole ie the combination of the heading and the Forest plot. The Panel did not consider that it was necessarily cherry picking of the data to include data from Kohno *et al* as cited in Pavlakis *et al* in the leavepiece rather than the other data cited by Roche. The Panel noted that patients in Kohno *et al* were within the Zometa licence and relevant to the leavepiece at issue ie they were women with stage IV breast cancer with at least one osteolytic bone metastasis. No breach of the Code was ruled.

Nor did the Panel consider that the heading 'Zometa reduces the risk of SREs' necessarily meant that only Zometa data could be shown. The Panel considered however that the Forest plot invited a direct comparison between Zometa and the other bisphosphonates shown; Zometa appeared to reduce the risk of SREs more than the other products mentioned. This was not the intention of the cited reference. The Panel considered this aspect was covered in another matter below. On the narrow basis that readers would understand that the Forest plot related to data for a number of bisphosphonates bearing in mind that there was a separate heading to the Forest plot and the medicines were identified the Panel ruled no breaches of the Code.

Roche alleged that only the first line of the Forest plot (Kohno *et al*) was relevant to the leavepiece about the use of Zometa in patients with metastatic bone disease from breast cancer. The rest of the Forest plot did not need to be used as it did not pertain to, or substantiate, the efficacy of Zometa, and was a breach of the Code.

The modifications and omissions made to the Forest plot were not necessary to comply with the Code; they exaggerated the relative efficacy of zoledronic acid and implied that statistically and clinically Zometa was better than the other bisphosphonates listed. The modifications distorted as to the significance of the study and gave a visually misleading impression. Modifications that Roche alleged to be in breach were the use of footnotes, inclusion of the red arrows not found in the original publication, the emphasis made to Zometa by highlighting it red, and omission of the patient numbers and weightings for every study. Roche explained that the original Forest plot depicted the relative efficacy of each bisphosphonate at its recommended dose(s) compared with placebo or no bisphosphonate and this was stated as part of the heading in the same font size as the text within the plot. In the adapted Forest plot, this part of the heading had been made into a footnote in a font size smaller than the main text. Therefore, it did not make it adequately clear that the depicted relative risk reduction of each bisphosphonate was vs placebo or no bisphosphonate. Further, the confidence intervals for Zometa and pamidronate almost completely overlapped as was the case for the other bisphosphonates depicted. As such, there was no statistical basis for inviting a comparison as was denoted by the red arrows added to the diagram to show risk reduction. In Case AUTH/2168/9/08 the Panel advised both parties of confidence interval overlap and lack of comparator statement and stated that no ruling could be made at that time as it had no complaint on these points. The fact that Novartis had ignored the Panel's concerns breached the spirit of the Code.

Further, the published Forest plot showed the patient numbers for every study. This was reflected in the size of the boxes depicting the relative risk and so the size of the studies relative to one another was clear and transparent. In Case AUTH/2168/9/08, the Panel ruled that Novartis had breached the Code because it had not reproduced the 'relative risk' boxes in this plot as in the original diagram in the Cochrane review or included the sample size of every study. The Forest plot in the leavepiece now at issue did not include the sample size of the treatment or control groups from any of the studies. Furthermore, the varying sizes of the boxes did not accurately reflect the size of the boxes in the original publication, as the box for Zometa was still larger, relative to the other boxes, than in the original paper. In addition, the red box for Zometa gave it undue prominence, relative to the black boxes for all the other medicines. Roche thus believed the immediate impression created by the Forest plot in the leavepiece was misleading. The Forest plot also disparaged other companies' products. In addition, Novartis' failure to modify the Forest plot according to the ruling in Case AUTH/2168/9/08 was a breach of undertaking in breach of Clause 2.

Roche believed that Novartis had used the Forest plot to claim superior efficacy by inviting a comparison of Zometa with the other bisphosphonates. Nowhere had Novartis stated that there were no randomized, controlled,

comparative trials as suggested by the Panel in Case AUTH/2168/9/08. The Panel had also acknowledged that the objective of Pavlakis *et al* was to examine bisphosphonates as a class; it was not designed to draw distinctions between any of the medicines studied. This was contrary to the visual impression created and failed to reflect all the available evidence. By using the Forest plot in this manner, Novartis had ignored the Panel and the spirit of the Code.

Roche alleged that, given all of the points raised by the Panel in Case AUTH/2168/9/08, the continued use of the adapted Forest plot from Pavlakis *et al* demonstrated Novartis' disregard for the spirit and letter of the Code in breach of its undertaking and as such in breach of the Code including Clause 2.

The Panel noted that Roche alleged that including data for bisphosphonates other than Zometa beneath the heading 'Zometa reduces the risk or SREs' was a breach of the Code. The Panel noted its ruling above. The Panel considered that the inclusion of data for other products beneath the claim was not unacceptable per se and on the narrow grounds alleged no breach of the Code was ruled.

With regard to the modification of the Forest plot, the Panel noted that the version in the leavepiece had a 'Risk Reduction' column added and for each product a percentage figure for the risk reduction was cited in a downward red arrow. The published Forest plot included only the risk ratio (plus 95% confidence intervals). The risk ratios were cited in an untitled column before the column headed 'Risk Reduction'. The Panel considered that the leavepiece did not faithfully reproduce the published Forest plot and had not been modified for the purpose of complying with the Code. A breach of the Code was ruled. This ruling was not appealed.

The Panel examined its rulings in the previous case, Case AUTH/2168/9/08, and reproduced relevant extracts which appeared in the full Panel ruling below.

The Panel considered the Forest plot in the leavepiece at issue in this case was different to the one at issue in Case AUTH/2168/9/08. The heading in the leavepiece 'Zometa reduces the risk of SREs' was different to the exhibition panel previously at issue which stated 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer.'

The leavepiece included some indication of size of the patient population by means of reproducing the size of various boxes used in the original publication. No actual patient numbers were included in the leavepiece although these were given in the published Forest plot.

The Panel noted that in Case AUTH/2168/9/08 the Forest plot was only ruled in breach in relation to the narrow allegation that it had been adapted so that all of the studies appeared to contain a similar number of patients in an attempt to mislead the reader that they all carried the same weight in breach of the Code. Novartis submitted that this had been addressed by the inclusion of the various sized boxes to reflect the sample sizes. The Panel considered, however, that this was insufficient as the prominent downward red 'risk reduction' arrows for each bisphosphonate were all of an equal size. In that regard the Forest plot misled as to the comparative size of the studies as before and a breach of the Code was ruled. In the Panel's view this represented a breach of the undertaking given in Case AUTH/2168/9/08; high standards had not been maintained. Breaches of the Code were ruled. Upon appeal by Novartis the Appeal Board noted the differences between the Forest plot now at issue, the Forest plot at issue in Case AUTH/2168/9/08 and the Forest plot as published by Pavlakis *et al*. The Appeal Board also noted the Panel's rulings in Case AUTH/2168/9/08. Turning to the current case, Case AUTH/2246/7/09, the Appeal Board noted that the promotional item at issue was a leavepiece which contained limited information. In the Appeal Board's view, Forest plots were a sophisticated way of presenting data and some readers would require a degree of explanation before they fully understood the data presented. The Appeal Board noted that Novartis had not appealed the Panel's ruling that the leavepiece did not faithfully reproduce the published Forest plot and had not been modified so as to comply with the Code. The Appeal Board considered that the Forest plot was misleading with regard to the comparative size of the studies as before; the downward red arrows added to this misleading representation. The Panel's rulings were upheld. The Panel considered that the failure to comply with the undertaking was such that Novartis had brought discredit upon and reduced confidence in the pharmaceutical industry; a breach of Clause 2 was ruled. Upon appeal by Novartis, however, the Appeal Board considered that some effort had been made to comply with the undertaking and the Panel's ruling was overturned. No breach of Clause 2 was ruled.

The Panel noted Novartis' submission as to how it had changed its material to take account of the previous ruling. The Panel noted, however, that its rulings had to reflect the complainant's allegations and the Panel's lack of comment about an aspect did not imply approval. In making its rulings the Panel could also not state precisely how a piece should be changed; it could not, in effect, pre-approve material.

The Panel noted that it had expressed concern about the impression of the exhibition panel in Case AUTH/2168/9/08. In the Panel's view it was clear that although it had only been able to make a ruling on the narrow grounds of the complaint it considered that any claim for superiority for Zometa vs other bisphosphonates, however depicted, could not be substantiated using the

Forest plot from Pavlakis *et al*. There had been no allegation in this regard and thus no rulings had been made. Thus in the case now before it, Case AUTH/2246/7/09, there could be no breach of undertaking in this regard and therefore no breaches of the Code including Clause 2 was ruled.

The Panel was extremely disappointed that it appeared that Novartis had not taken notice of the Panel's wider comments in Case AUTH/2168/9/08 about the Forest plot. This was disingenuous and unacceptable. The fact that the heading had been changed did not in the Panel's view mean that the Forest plot in itself did not imply superiority for Zometa vs the other bisphosphonates listed. In the Panel's view any graph/diagram etc which incorporated data for a number of medicines inevitably invited a direct comparison of those medicines. The leavepiece at issue thus visually misled the reader; it invited a direct comparison between the products and implied superiority of Zometa vs other bisphosphonates. It was not known if the differences between the products were statistically or clinically significant. Pavlakis *et al* was not designed to draw distinction between any of the medicines contrary to the impression given. The Panel ruled breaches of the Code. The Panel considered that the Forest plot in the leavepiece disparaged other companies' products. A breach of the Code was ruled.

Roche stated that on 13 March 2009, one of its employees, a pharmacist, had asked Novartis to email a copy of a poster, Hoer *et al* (2005), cited as a supporting reference in the leavepiece, but nothing was received. After the third request a 2005 conference abstract, but not the poster, was provided twelve working days from the date of the original request. The first time the pharmacist received the actual poster was as an attachment to Novartis' inter-company correspondence dated 11 May. Roche alleged that Novartis' failure to supply the references to support the claims made in its leavepiece within ten working days was in breach of the Code.

In addition, on 2 April 2009 the pharmacist requested another poster (Heatley *et al*, 2006) also referenced in the leavepiece. Novartis supplied an abstract but a second request for the poster was not acknowledged. The first time the poster was provided was as an attachment to the letter from Novartis dated 11 May, over a month after the original request, again in breach of the Code.

The abstracts did not substantiate the claims in the leavepiece. Roche alleged that as the pharmacist was a health professional and entitled to be provided, within ten working days, with information to substantiate materials, as outlined in the Code, Novartis had failed to maintain high standards in breach of the Code including Clause 2.

As Novartis was unable to provide the first poster in a timely manner, Roche conducted a literature search and found a 2006 analysis of the study with data which differed from that published in the 2005 abstract. As the most recent Hoer *et al* data had not been used, Roche alleged that the data had been cherry-picked.

The Panel noted that there was no exemption for proof of substantiation to be provided within ten working days for health professionals employed by pharmaceutical companies. The Panel was sympathetic to Novartis' view that its medical information department would prioritise requests from clinicians. With regard to the provision of Hoer *et al*, there appeared to be a difference between the parties; Roche stated that it had only received the poster as part of the inter-company dialogue and Novartis stated that the abstract had been sent on 20 and 30 March. According to Novartis, Hoer *et al* (2005) had been incorrectly cited in the leavepiece by omitting to state the material was a poster.

The Panel noted that Novartis had provided the Hoer *et al* abstract to Roche on 30 March. It was not entirely clear from Novartis' records exactly what had been sent. An allegation that the abstract failed to substantiate the claims would be considered below. Substantiation had been sent by post within ten working days and followed up by email when Roche contacted Novartis again. It appeared that the copy sent in the post had not been received. In the circumstances the Panel ruled no breach of the Code.

Novartis accepted that the second poster had not been sent. As Roche had, in effect, requested substantiation, the Panel ruled a breach of the Code as substantiation had not been provided in response to a request from a health professional. The Panel did not consider that the failure to supply the poster meant that high standards had not been maintained nor that Novartis had brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of the Code including Clause 2 was ruled.

The Panel noted the difference between Hoer *et al* (2005) and the 2006 data, this being 1% more patients still on therapy at 6 months ie 36% in 2006 instead of 35% in the 2005 publication. The Panel did not accept that Novartis had cherry-picked the data as alleged. No breach of the Code was ruled.

Roche noted that page 3, headed 'There are compliance issues with oral bisphosphonates', featured a graph headed 'Compliance with oral bisphosphonates' which depicted discontinuation rates at 3 months (44%) and 6 months (65%). The graph was adapted from the poster Hoer *et al* and was a retrospective observation study of health insurance claims. Roche considered the presentation of the data from Hoer *et al* was misleading. The leavepiece was for use with health professionals involved in the treatment and management of patients with metastatic bone disease from breast cancer. Hoer *et al* could not substantiate claims about such patients as it

comprised a mixed population of men and women with differing diagnoses only 58/497 (11.7%) of which had breast cancer with bone metastases. Evidence suggested that adherence and persistence to oral therapy was better in cancer patients vs patients who had non-oncological chronic disease. Furthermore, it was not possible from the data reported in the poster to know which treatments the patients with breast cancer received; and because the persistency rates were not reported by diagnosis it was not clear from the poster or leavepiece what the persistency rate was in the 58 breast cancer patients with metastatic bone disease. The claims made from this reference were misleading and not substantiated by the data supplied.

The Panel noted that Hoer *et al* was a retrospective observational study using data from health insurance claims. Not all the patients had advanced malignancies involving bone. 109 of the 497 patients had bone metastasis. There were a number of limitations listed including that the analysis was limited to the outpatient prescriptions of oral bisphosphonates. The study stated that the risk of being not persistent with therapy was higher for patients with bone metastasis than without such a diagnosis.

The Panel noted that only one of the four oral bisphosphonates used, clodronate, was licensed in the UK for use in cancer patients with bone metastases. The only other oral bisphosphonate so licensed in the UK was Roche's product Bondronat, but this had not been included in the study.

The Panel considered that the heading 'There are compliance issues with oral bisphosphonates' was not unreasonable per se. The Panel considered, however, that given the leavepiece was specifically about patients with metastatic breast cancer the graph would be assumed to apply to the use of bisphosphonates available in the UK for the prevention of SREs in that patient group. The data was not so limited and thus the graph and specific discontinuation claims at 3 and 6 months were misleading and had not been substantiated. Breaches the Code were ruled. The Panel did not consider that the comparison between iv Zometa and oral bisphosphonates was misleading per se and no breach of the Code was ruled. The graph did not give a fair and balanced view of the data and thus a breach of the Code was ruled.

Roche considered that the heading 'There are compliance issues with oral bisphosphonates', use of Hoer *et al* and the overall impression created when page 3 was viewed with the Forest plot on the facing page, was that all oral bisphosphonates were the same which was all-embracing, incapable of substantiation, created confusion and misled the reader both by the visual impression given and as to the significance of Hoer *et al*. The title disparaged oral Bondronat, as the market leading oral bisphosphonate, by the overall impression created and the all-embracing claims. Roche alleged that use of these data in this manner was inappropriate, failed to maintain high standards and brought discredit to the pharmaceutical industry.

The Panel noted its comments about Hoer *et al* and its rulings above which covered many of the allegations here. The Panel considered that the heading in the context of the graph was disparaging and all-embracing. Breaches of the Code were ruled.

The Panel noted that the leavepiece was clearly promotional material and not sponsored material and it ruled no breach of the Code.

The Panel considered that high standards had not been maintained and ruled a breach of the Code. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 and ruled accordingly.

Roche noted that directly beneath the graph on page 3 were the following three quotations; 'Because IV bisphosphonates are administered in a hospital or infusion centre, compliance with therapy is not a concern' (Heatley *et al*); 'Oral administration requires precautionary measures to ensure absorption and – for some [bisphosphonates] – to avoid gastrointestinal adverse events' (Aapro *et al*) and 'If not taken properly, oral bisphosphonates can cause a high incidence of [gastrointestinal] adverse events, including esophagitis, mucositis, nausea, vomiting and diarrhoea, and may exacerbate this side effects of anticancer therapy' (Conte and Guarneri).

Roche believed readers would consider the quotations immediately below the graph from Hoer *et al* to directly refer to that study. Roche alleged that the quotation, 'Oral administration requires precautionary measures to ensure absorption and – for some [bisphosphonates] – to avoid gastrointestinal adverse events', was taken out of context. Particularly as the sentence following it was referenced to a study about compliance of bisphosphonate therapy in patients with osteoporosis rather than metastatic bone disease from breast cancer. Roche alleged that the quotations and the context in which they were used were misleading as they did not accurately and clearly reflect the studies in question nor the overall meaning of the authors. The quotations were taken out of context, unbalanced, misled as to their overall significance and disparaged oral Bondronat. This did not allow the reader to form their own opinion of the therapeutic value of oral bisphosphonates for the treatment of patients with metastatic bone disease and thereby failed to maintain high standards. The quotations were misleading, disparaging and cherry picked the data.

The Panel considered that it was clear from the leavepiece that the quotations were from different studies. The Panel did not consider that the readers would assume that the quotations applied to the

discontinuation data from Hoer *et al*. In the Panel's view the quotations referred to general compliance issues with oral bisphosphonates.

The Panel did not agree that the quotation from Aapro *et al* was out of context given the next sentence referred to its use in oestoporosis. Precautions to ensure absorption of oral bisphosphonates and to avoid gastrointestinal events would apply whatever the diagnosis. Oral Bondronat was to be taken after an overnight fast of at least six hours and before the first food or drink of the day. Fasting had to continue for at least 30 minutes after taking the tablet and patients should not lie down for 60 minutes after taking the tablet. The Panel did not consider that the quotations disparaged Bondronat. Nor were they misleading or cherry picking the data as alleged. The Panel ruled no breach of the Code. The quotation was faithfully reproduced and accurately reflected the meaning of the authors. No breach of the Code was ruled.

The Panel did not consider that the quotation from Heatley *et al* 'Because IV bisphosphonates are administered in a hospital or infusion centre, compliance with therapy is not a concern' had been taken out of context or was misleading. No breach of the Code was ruled. The quotation was clearly about iv bisphosphonates and not linked to the Hoer *et al* data in the graph above it. The Panel did not consider that the quotation was clearly cherry picking of the data as alleged or that it disparaged Bondronat as alleged. No breach of the Code was ruled. In the Panel's view the quotation was faithfully reproduced and accurately reflected the meaning of the authors. No breach of the Code was ruled. The alleged breach of the Code in relation to the Heatley study was considered above.

The Panel similarly considered that the quotation from Conte and Guarneri had not been taken out of context, was not misleading and did not disparage Bondronat. In the Panel's view the quotation accurately reflected the meaning of the authors. No breaches of the Code were ruled.

Roche complained about a leavepiece for Zometa (intravenous (iv) zoledronic acid) issued by Novartis. Zometa was indicated, *inter alia*, for the prevention of skeletal related events (SREs) (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone. The leavepiece was about metastatic breast cancer.

Roche marketed iv and oral Bondronat (ibandronic acid). Both formulations were indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.

Inter-company dialogue had not been successful.

As Roche had alleged a breach of undertaking this aspect of the complaint was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

1 Strapline 'Protects them to the bone'

The strapline appeared as part of the Zometa brand logo on pages 1 and 3 of the leavepiece.

COMPLAINT

Roche alleged that the strapline 'Protects them to the bone' directly and indirectly implied that Zometa prevented bone metastases.

As stated in the prescribing information Zometa was licensed for the treatment of tumour-induced hypercalcaemia and prevention of SREs in patients with advanced malignancies involving bone. The word 'to' expressed motion or direction toward a point, person, place, or thing approached and reached. Therefore, 'Protects them to the bone' could be interpreted to mean that Zometa prevented bone metastases from occurring in the first place, rather than preventing SREs, such as fractures, in breast cancer patients already diagnosed with advanced malignancies involving bone. This misled the reader both by distortion and exaggeration, potentially leading to inappropriate and unfounded expectations on the part of the health professional and patient in terms of the clinical value and impact of Zometa. Roche alleged that the strapline was all-embracing, ambiguous and incapable of substantiation in breach of Clauses 7.2, 7.4 and 7.10.

In addition, Roche did not believe that this potential meaning of the strapline was substantiated by the Zometa summary of product characteristics (SPC). It could be interpreted as a 'teaser' to elicit interest in the expected licence for Zometa adjuvant therapy to prevent bone metastases, which was currently being considered by the European Medicines Evaluation Agency (EMEA). This application was based on study data which had been presented to several major oncology congresses (Gnant *et al* 2008, Gnant *et al* 2009, Ougari *et al* 2009) and were therefore familiar to many of the leavepiece's audience.

This constituted promotion of a medicine in an area where it did not have a marketing authorization in breach of Clauses 3.1, 3.2, 9.1 and 9.2. Moreover, the strapline failed to maintain high standards and brought discredit upon and reduced confidence in the industry in breach of Clause 2.

RESPONSE

Novartis believed that Roche had misinterpreted the strapline 'Protects them to the bone'. 'To' reflected the rapid take up and binding of Zometa to mineralised bone as substantiated by pharmacokinetic data cited in Section 5.2 of the Zometa SPC ie 'Over the first 24 hours, 39 ± 16% of

the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue'.

During inter-company dialogue Roche referred to the phrase as 'could be misinterpreted', demonstrating that this was its interpretation. Novartis considered that clinicians experienced in the use of bisphosphonates would consider the strapline only in relation to the prevention of SREs and treatment of tumour-induced hypercalcaemia. Both indications were within Zometa's current licence.

Novartis submitted that Roche's interpretation that the strapline meant that Zometa prevented bone metastases from occurring was a further misinterpretation and misrepresentation of its meaning. Even if Roche's interpretation of the strapline was to cover an anti-tumour effect, which was not Novartis' use or view of the strapline, Novartis noted that Section 5.1 of the Zometa SPC stated; 'In addition to being a potent inhibitor of bone resorption, zoledronic acid also possesses several anti-tumour properties that could contribute to its overall efficacy in the treatment of metastatic bone disease'. Therefore, the data would substantiate the concern raised by Roche.

Novartis noted that there should be a reasonable expectation that competitors only complained if, having fully researched and considered all associated evidence, they continued to have a reasonable belief that claims could not be substantiated or that health professionals were being misled. This thorough evaluation of all the information did not appear to have been the case here.

In preventing SREs, Zometa clearly offered bone protection. This was supported by Section 5.1 of the SPC and the results of several randomised controlled trials. The Panel had noted in Case AUTH/2168/9/08 that the selective action of bisphosphonates on bone was based on their high affinity for mineralised bone. The use of the word 'protects' was clearly in the context of protecting patients from the effects of both tumour-induced hypercalcaemia and SREs in patients with advanced malignancy.

Novartis firmly rejected Roche's allegation that the strapline was a 'teaser' to elicit interest in the expected licence for Zometa as adjuvant therapy to prevent bone metastases.

Novartis did not believe that the strapline was in breach of Clause 9.1 or 9.2 as there was no reasonable expectation that a health professional would draw the same conclusions as Roche. As such it did not tease the recipient by eliciting an interest in something which would follow, or would be available at a later date, without providing any actual information about it (supplementary information to Clauses 9.1 and 9.2). Furthermore the strapline did not promote any future licence, real or perceived. As the strapline could be substantiated by the Zometa licence and the SPC, Novartis denied breaches of Clauses 2, 3.1, 3.2, 7.2, 7.4, 7.10, 9.1 and 9.2.

PANEL RULING

The Panel noted that the front page of the leavepiece was headed 'Fight skeletal destruction with Zometa'. Attached to a stylised picture of a hip joint with a bone metastases and apparent radiating fractures was the claim 'Patients with metastatic breast cancer lead a fragile existence Handle with Zometa'. The product logo and strapline at issue, 'Protects them to the bone' appeared in the bottom right hand corner.

The Panel noted that Zometa was currently indicated, *inter alia*, to prevent SREs in patients with advanced malignancies involving bone. The Panel noted the target audience for the leavepiece but nonetheless considered that the strapline was ambiguous. Some readers might consider that it meant that Zometa could be used to protect bone from metastases and this was not so. Some readers might be familiar with reports of the antimetastatic activity of zoledronic acid (Gnant *et al* 2008). Roche had submitted that Zometa as adjuvant therapy to prevent bone metastases was being considered by the EMEA although Novartis had not commented on this point. Overall the Panel considered that the meaning of the strapline was opaque such that it was inconsistent with the SPC and a breach of Clause 3.2 was ruled. The Panel did not consider that the strapline amounted to promotion prior to the grant of the marketing authorization and no breach of Clause 3.1 was ruled. The promotion of an unlicensed indication was prohibited by Clause 3.2 and thus covered by the Panel's ruling above. The strapline was misleading and not capable of substantiation and as a result did not encourage the rational use of the medicine. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled. The strapline was not a teaser as the medicine was available and information about it had been given. The Panel considered that, nonetheless, overall high standards had not been maintained and a breach of Clause 9.1 was ruled. The strapline in itself had not failed to recognise the special nature of medicines and the professional standing of the audience. Nor was it likely to cause offence. No breach of Clause 9.2 was ruled. The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2; no breach of Clause 2 was thus ruled.

APPEAL FROM NOVARTIS

Novartis submitted that the strapline in its current context accurately reflected the marketing authorization for Zometa and was consistent with the SPC. It was not ambiguous or opaque. The strapline appeared initially on the front page of the leavepiece and subsequently on page 3. The front page was entitled 'Fight skeletal destruction with

Zometa'. Attached to a stylised picture of a hip joint with fractures radiating from a bone metastasis was the claim 'Patients with metastatic breast cancer lead a fragile existence. Handle with Zometa'. The product logo and strapline at issue, 'Protects them to the bone', appeared in the bottom right hand corner. The strapline should be interpreted in the context of the page on which it appeared and the leavepiece as whole ie in the setting of metastatic breast cancer where pre-existing metastases lead to bone fracture. This context was clearly stated on the cover and was the main theme of the leavepiece. The leavepiece was designed to tell clinicians what they could do for a patient with metastatic cancer in their bones. Novartis submitted that it could not be read to be about what clinicians could do to prevent the formation of bone metastases. Novartis submitted that the latter interpretation, on which the Panel based its ruling, could not be sustained on the evidence of the leavepiece taken as whole. The stylised picture itself implied that Zometa protected against pathological fractures (SREs) caused by metastases to bone. The picture did not suggest to the target audience of sophisticated hospital specialists that Zometa protected against the formation of metastases. All of this was consistent with the therapeutic indications section of the Zometa SPC (Section 4.1). Such consistency was noted by the Panel but Novartis considered this had not been given sufficient consideration. The strapline should not have been considered in isolation. Consideration should be given to the primary target audience in the first instance rather than a minor ill defined secondary audience who could be misled by the material.

Novartis noted that information on the status of any extension to the licensed indications for Zometa was commercially confidential. Such information could be provided separately in confidence. It was public knowledge that Zometa was under investigation in randomised controlled clinical trials for any potential anti-tumour activity. Gnant *et al* 2008 did not show any statistical improvement in the number of metastases in breast cancer following treatment with Zometa but showed statistical improvements in disease free and progression free survival. Thus, the specialist audience would be sufficiently well informed and not misled into the conclusion that Zometa prevented the spread of tumour cells to the bone. This would be an incorrect inference given the findings of Gnant *et al* (2008) but it was, nevertheless, the conclusion drawn by both Roche and the Panel. Novartis submitted that the Panel's conclusion in this regard could not stand. Novartis did not consider that the target audience was likely to have been misled. Novartis submitted that the leavepiece was not in breach of Clauses 7.2, 7.4 or 7.10 and so would not have breached Clause 9.1.

Novartis submitted that the strapline was consistent with the Zometa SPC. Zometa was indicated to prevent and, therefore, to protect patients against pathological fractures caused by pre-existing bone metastases. This was clearly conveyed in the strapline 'Protects them to the bone'. The close proximity of the prescribing information on page 4 of the leavepiece was also relevant to Novartis' submission that neither the strapline, the picture nor the leavepiece as a whole was misleading or inconsistent with the SPC. The prescribing information clearly stated the indications for which Zometa held a marketing authorization.

Novartis submitted that the strapline 'Protects them to the bone' was wholly consistent and capable of substantiation against the Zometa SPC. The notion of protection conveyed in the strapline was directly and clearly derived from and substantiated by the therapeutic indications section of the Zometa SPC (Section 4.1) which stated: 'Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone', and was supported by clinical studies in the SPC. Novartis submitted that 'prevention' implied a pre-emptive effect on the pathological actions of metastases on bone. The statement 'Protects them to the bone' was a natural, reasonable and justifiable interpretation of this pre-emptive action. The SPC was as clear as it could be that Zometa was indicated in the 'prevention' of skeletal related events.

Novartis submitted that the effect on bone was also clearly reflected in and substantiated by the Zometa SPC. Novartis noted that Section 5.1 of the SPC stated 'Zoledronic acid belongs to the class of bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclastic bone resorption. The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear'.

Novartis submitted that the SPC thus described the high affinity of Zometa both for bone and its strong osteoclastic inhibitory properties which justified use of the word 'bone' in the strapline. 'To' in the strapline also reflected the rapid uptake and binding of Zometa 'to' mineralised bone as substantiated by pharmacokinetic data for Zometa. Section 5.2 of the Zometa SPC stated that following intravenous (iv) infusion with Zometa 'Over the first 24 hours, 39 ± 16% of the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue'. This reflected the rapid take up from the iv compartment 'to' bone and the binding of Zometa 'to' mineralised bone.

Novartis submitted that the strapline 'Protects them to the bone' was, thus, wholly consistent with the Zometa SPC and marketing authorization and properly reflected the scientific studies which underlined those documents as approved by the relevant regulatory authority. Novartis submitted that no breach of Clause 3.2 could be established on these facts.

Novartis submitted that as the claim was fair,

balanced and unambiguous there had been no breach of Clause 7.2. The strapline could be substantiated by the Zometa SPC and, thus, there had been no breach of Clause 7.4. The strapline did not encourage irrational use of the medicine and thus no breach of Clause 7.10. High standards had been maintained and there had been no breach of Clause 9.1.

RESPONSE FROM ROCHE

Roche alleged that the licensed patient population of patients with bone metastases was not stated clearly. The most obvious interpretation of 'Protects them to the bone' was prevention of bone metastases which was not consistent with the licensed indication. The claim did not encourage rational use of the medicine. All the points together indicated high standards had not been maintained. Roche alleged that the strapline breached Clauses 3.2, 7.2, 7.4, 7.10 and 9.1.

Novartis argued that the claim 'Protects them to the bone' accurately reflected the Zometa marketing authorization. However, nowhere on the leavepiece (other than in the prescribing information) was it clearly stated that the licensed indication for Zometa was the treatment of patients with advanced malignancies already involving bone. The front page referred to 'Patients with metastatic breast cancer' not 'Patients with metastatic bone disease' or 'Patients with advanced malignancies involving bone' in line with the indication. The Medicines and Healthcare products Regulatory Agency (MHRA) emphasised strongly this key point in its' 'Tips for prevetting of promotional material' ie 'The importance of clearly stating the authorized indication of the product. This helps to ensure that the claims made are set in a clear context.' This point had been emphasised in each of the MHRA's annual reports on advertising. This suggested deficiencies in training and knowledge as well as the thoroughness of the review of materials, and the standards expected by the MHRA had not been maintained. As the indication, and/or population for which Zometa was indicated, was not clearly stated the claims made in the leavepiece were not set in a clear context, which could encourage misinterpretation and inappropriate use of the medicine. High standards did not appear to have been maintained.

A key element of marketing could be wordplay and double meanings; however these should never mislead. Regrettably, as was the convention with straplines, 'Protects them to the bone' was not referenced. Referencing might have provided some clear direction as to Novartis' intention for the interpretation of the claim. Roche submitted that there were at least four possible interpretations of 'Protects them to the bone' some of which were actively misleading:

1 Zoledronic acid targeted bone.
2 An effect in line with the licensed indication to protect against skeletal related events in those with bone metastases.
3 An effect in preventing the development, or prophylaxis, of bone metastases.
4 A more general effect on the tumour and/or metastases generally.

Roche alleged that had the claim been 'Protects bone' then the meaning could have been straightforward and clear. However the inclusion of 'them to' made the claim far less transparent. The key to the interpretation of the claim appeared to lie in the meaning of the word 'to.' Also, in deciding which was the most likely interpretation by health professionals it was important to consider not only the context in the material itself but also the wider context of the scientific literature, congresses and the like. 'To' in the context of the claim could mean 'in the direction of' bone or be the boundary of an effect as in 'soaked to the skin' or 'rotten to the core.' Neither of these was consistent with interpretation 2 above and the licensed indication. The former was consistent with interpretation 3 and the latter with interpretation 4. Contrary to Novartis' appeal Roche did not believe that Zometa's uptake and binding by bone was an obvious interpretation of the claim, because of the construction of the phrase.

Roche alleged that as already discussed this leavepiece did not clearly set out the population for which Zometa was indicated. The patient population stated on the leavepiece in question was 'Patients with metastatic breast cancer.' Patients with metastatic breast cancer might not already have bone metastases and so the interpretation of prophylaxis of bone metastases was certainly likely, if not encouraged. The inclusion of the indication in the prescribing information was insufficient to define the eligible patient population for Zometa given the broader descriptor, 'Patients with metastatic breast cancer', on the front cover. Promotional material itself must comply with Clause 7.2 and be accurate and unambiguous.

Roche alleged that in the wider context beyond the leavepiece, there had been much discussion in the literature, at satellite symposia and conferences of clinical trials to prevent bone metastases, and even data suggesting effects of Zometa on soft tissue metastases and the tumour itself by inducing apoptosis or inhibiting angiogenesis (Aapro *et al* 2008, Bedard *et al* 2009, Winter *et al* 2008, Doggrell 2009, Coleman 2009, Novartis CIBD satellite 2008). Bedard *et al* even suggested that patients receiving adjuvant ovarian suppression should have the possible reductions in the risk of breast cancer relapse discussed with them. Bedard *et al* concluded 'There is reason to believe that newer generation bisphosphonates may deliver greater efficacy [than clodronate] and effects outside bone.' Zoledronic acid was described as providing a hostile soil for the tumour seed. Roche therefore disagreed with Novartis' assertion that the primary target audience would not be misled by the material. A less well informed audience might interpret the claim 'Protects them to the bone'

literally ie Zometa prevented spread of breast cancer to bone. However, a more informed audience would be aware of the data and debate relating to prevention of spread to bone and potential extra-skeletal effects on tumours and interpret the claim in a much broader way.

Roche alleged that Novartis had not adequately addressed the fundamental issues with this claim. It was not obvious what it meant. The literal meaning would constitute promotion outside of the licensed indication in breach of Clause 3.2. It was misleading, not substantiable and did not encourage rationale use in line with the SPC in breach of Clauses 7.2, 7.4 and 7.10. Given the context of the development of Zometa for adjuvant use and the literature in the area, utmost care was required to avoid misinterpretation of claims. This care did not seem to have been taken; high standards were not maintained and a ruling of a breach of Clauses 3.2, 7.2, 7.4, 7.10 and 9.1 was justified.

APPEAL BOARD RULING

The Appeal Board noted that the front page of the leavepiece was headed 'Fight skeletal destruction with Zometa'. Attached to a stylised picture of a hip joint with a bone metastases and emerging rays was the claim 'Patients with metastatic breast cancer lead a fragile existence Handle with Zometa'. Some members of the Appeal Board thought the emerging rays signified metatastic activity rather than fractures as described by the Panel. The product logo and strapline at issue, 'Protects them to the bone' appeared in the bottom right hand corner. It also appeared on page 3 of the leavepiece.

The Appeal Board noted that Zometa was currently indicated, *inter alia*, to prevent SREs in patients with advanced malignancies involving bone. The Appeal Board noted that approximately 65% of patients with metastatic breast cancer had bone metastases. It followed, therefore, that approximately 35% of patients with metastatic breast cancer would not have bone involvement; these patients would not be suitable for Zometa therapy. The Appeal Board considered that the front page of the leavepiece did not make it clear that Zometa was indicated to prevent skeletal fracture when bone metastases were already present. Some readers might consider that Zometa could be used to protect bone from metastases and this was not so. Overall the Appeal Board considered that the meaning of the strapline was ambiguous such that it was inconsistent with the particulars listed in the SPC. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The strapline was misleading and not capable of substantiation and as a result did not encourage the rational use of the medicine. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.4 and 7.10. The appeal on these points was unsuccessful.

The Appeal Board noted its rulings above but nonetheless did not consider that high standards had not been maintained and no breach of Clause 9.1 was ruled. The appeal on this point was successful.

2 Claim 'Zometa reduces the risk of SREs'

The claim appeared as the heading to page two of the leavepiece which depicted a Forest plot headed 'Overall risk of skeletal events in advanced cancer by individual drug at recommended dosing'. The claim was referenced to Pavlakis *et al* (2005) a Cochrane Review on Bisphosphonates for Breast Cancer. The Forest plot included risk reduction figures and p values from a number of studies for Zometa, iv pamidronate, iv ibandronate, oral ibandronate and oral clodronate vs placebo or no treatment. A footnote below the Forest plot stated that it was adapted from Pavlakis *et al* and that 'Original trials may have had different endpoints'.

COMPLAINT

Roche was concerned about the context in which the claim 'Zometa reduces the risk of SREs' was used.

In inter-company dialogue, Novartis had stated that the heading was supported by Pavlakis *et al* and the Zometa SPC, Section 5.1. This detailed the two clinical trials that supported the licence for the use of Zometa in the prevention of SREs in patients with breast cancer; the placebo-controlled trial by Kohno et al (2005) and a randomized, double-blind trial demonstrating comparable efficacy of zoledronic acid vs pamidronate in the prevention of SREs. Roche questioned why Novartis had not included the Kohno data and the Level 1 evidence from the trial vs pamidronate but instead had presented a meta-analysis which only contained a single study of Zometa and several studies of other agents. The Zometa trial shown in the Forest plot included only 228 Japanese women for whom no other bisphosphonates were available at that time. This population was not comparable with the UK population for which Zometa was being promoted and Roche questioned why this population alone should be used to promote a UK marketed medicine, when other Level 1 evidence in a European population was available. This constituted cherry picking of data in breach of Clause 7.2.

If, as submitted by Novartis, the heading was clearly supported by line 1 in the Forest plot, then only the top row of the Forest plot, which related to Zometa (Kohno *et al*) needed to be included. There was no reason to include the rest of the Forest plot, which did not substantiate the efficacy of Zometa nor was it supported by the heading, unless Novartis intended to make a claim for efficacy of Zometa compared with other bisphosphonates. This was contrary to the Panel's comments in Case AUTH/2168/9/08 and contravened the spirit of the Code. Roche maintained that overall the heading, in conjunction with the Forest plot, suggested superior efficacy of Zometa vs other bisphosphonates. This

was misleading and incapable of substantiation. The Cochrane review was a meta-analysis of bisphosphonates as a class and was not designed to draw comparisons between the various bisphosphonates as highlighted by the Panel in Case AUTH/2168/9/08.

In Case AUTH/2177/10/08 (Allergan vs Merz) the Panel had stated, 'Nonetheless the Panel considered that even when a claim was true the context in which it was used was very important'. Roche believed the overall impression created by the page implied a comparison between Zometa and other bisphosphonates and a claim for superior efficacy which was not the intention of Pavlakis *et al*. Therefore, the heading, 'Zometa reduces the risk of SREs' in the context in which it was used was an unbalanced reflection of the data presented, misled the reader and was incapable of substantiation by Pavlakis *et al* to which it was referenced. The page neither included data solely on Zometa nor made it clear and transparent from the title that the graph related to bisphosphonates as a whole and was in breach of Clauses 7.2 and 7.4.

RESPONSE

Novartis considered Roche's statements to be inaccurate and failed to interpret the Code correctly.

Novartis stated that substantiation need not be provided in relation to the licensed indications. Section 5.1 of the Zometa SPC supported the licensed indications. Pavlakis *et al* further supported the heading 'Zometa reduces the risk of SREs' which was an acceptable heading for this page. Use of an independent meta-analysis in promotional material was a well accepted method to demonstrate efficacy of a medicine in a therapeutic field, especially in the absence of head-to-head studies and was accepted by the Panel in Case AUTH/2168/9/08. The data would be considered by the reader under the heading 'Zometa reduces the risk of SREs' and was not, as alleged by Roche, an invitation to compare Zometa with other bisphosphonates. Furthermore, Novartis believed additional comments made by the Panel in Case AUTH/2168/9/08 regarding the meta-analysis graphic related specifically to its use under the heading 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer'.

The leavepiece now at issue was wholly concerned with metastatic breast cancer, and the benefit Zometa might, in that context, have in preventing SREs.

Case AUTH/2177/10/08 was not relevant to this case. There was no attempt to have the reader consider other bisphosphonates in the table presented on Page 2 or claim superior efficacy for Zometa. The data was neither misleading nor an unbalanced reflection of the Cochrane meta-analysis which stated that Zometa was as effective as pamidronate in the prevention of SREs.

Also as recognised by the Panel in Case AUTH/2168/9/08, the Code did not require the claim in question to be referenced. The claim had to be capable of substantiation, not misleading and otherwise comply with the Code. Novartis believed the claim met this requirement and denied breaches of Clauses 7.2 and 7.4.

Novartis believed that in citing Case AUTH/2177/10/08 Roche knew the implications of that case. Novartis was specifically ruled in breach of Clause 7.8 for not using the appropriately sized boxes to reflect the study sample sizes. Therefore Novartis was surprised that in being familiar with this case Roche continued to contend that Novartis had not complied with the undertaking given in Case AUTH/2168/9/08. Roche would be aware that the Appeal Board had noted that no specific ruling had been made with regard to the image and consequently the Appeal Board did not consider that Merz Pharma had breached its undertaking and no breach of the Code was ruled.

PANEL RULING

The Panel considered that the heading 'Zometa reduces the risk of SREs' in itself was not unreasonable. The allegations related to the page as a whole ie the combination of the heading and the Forest plot. The Panel did not consider that it was necessarily cherry picking of the data to include data from Kohno *et al* as cited in Pavlakis *et al* in the leavepiece rather than the other data cited by Roche. The Panel noted that patients in Kohno *et al* were within the Zometa licence and relevant to the leavepiece at issue ie they were women with stage IV breast cancer with at least one osteolytic bone metastasis. The results of the study were cited in the Zometa SPC. No breach of Clause 7.2 was ruled.

Nor did the Panel consider that the heading 'Zometa reduces the risk of SREs' necessarily meant that only data for Zometa could be shown. The Panel considered however that the inclusion of the Forest plot invited a direct comparison between Zometa and the other bisphosphonates shown; Zometa appeared to reduce the risk of SREs more than the other products mentioned. This was not the intention of the cited reference. The Panel considered this aspect was the subject of Point 3 below. On the narrow basis that readers would understand that the Forest plot related to data for a number of bisphosphonates bearing in mind that there was a separate heading to the Forest plot and the medicines were identified the Panel ruled no breach of Clauses 7.2 and 7.4.

3 The use of the Forest plot from Pavlakis *et al*

COMPLAINT

Roche alleged that the overall impression created by the Forest plot from Pavlakis *et al*, the manner in which it had been adapted from the original publication, and its proximity to the claim 'Zometa

reduces the risk of SREs', placed undue emphasis on the efficacy of Zometa compared with other bisphosphonates. It also invited the reader to directly compare the studies shown, many of which were of a bisphosphonate vs placebo or no bisphosphonate.

The way in which the Forest plot was modified misled as to the nature of the study and exaggerated the results; it suggested to the reader that the meta-analysis was designed to compare the efficacy of bisphosphonates in their class which was not so. The objective of the analysis was to assess the effect of bisphosphonates in women with metastatic bone disease as stated by the Panel in Case AUTH/2168/9/08.

Moreover, Clause 7.8 clearly stated that graphs and tables should only be included if they were relevant to the claims and comparisons being made. Only the first line of the Forest plot (Kohno *et al*) was relevant to the leavepiece about the use of Zometa in patients with metastatic bone disease from breast cancer. Therefore, Roche did not consider there was any reason for the remainder of this Forest plot to be used in such promotional materials as it did not pertain to, or substantiate, the efficacy of Zometa, and was a breach of Clause 7.8.

Furthermore, the modifications and omissions made to the Forest plot were not necessary to comply with the Code and simply exaggerated the relative efficacy of zoledronic acid in its class, implying that statistically and clinically Zometa was better than the other bisphosphonates listed. The supplementary information to Clause 7.8 stated, 'If a graph, table or suchlike is taken from a published study it must be faithfully reproduced except where modification is needed in order to comply with the Code'. It was clear that the modifications were not made for this purpose, they distorted as to the significance of the study and gave a visually misleading impression in breach of Clause 7.8.

Novartis had rejected further modifications requested by Roche as they added little. Roche highlighted that the supplementary information to Clause 7.8 also stated that published data should be faithfully reproduced, care should be taken with graphs to ensure that they did not mislead by their incompleteness and graphs must be adequately labelled so that the information could be readily understood.

The Code was clear that graphs etc should be accurately reproduced thereby enabling the reader to form their own opinion of the data. Novartis had omitted vital details necessary to enable the reader to form their own opinion of the data. Novartis' apparent lack of understanding around the use of published data enhanced Roche's concerns regarding the company's comprehension and implementation of the Code, standard operating procedures and approval processes.

Modifications that Roche alleged to be in breach were the use of footnotes, inclusion of the red arrows not found in the original publication, the emphasis made to Zometa by highlighting it red, and omission of the patient numbers and weightings for every study. Roche detailed its concerns below.

The original Forest plot depicted the relative efficacy of each of the available bisphosphonates at their recommended doses compared with placebo or no bisphosphonate and this was stated as part of the heading in the same font size as the text within the plot. In the adapted Forest plot, this part of the heading had been moved from this prominent position and made into a footnote in a font size smaller than the main text. Therefore, it did not make it adequately clear that the depicted relative risk reduction of each bisphosphonate was compared to placebo or no bisphosphonate. Further, the confidence intervals for Zometa and pamidronate almost completely overlapped as was the case for the other bisphosphonates depicted. As such, there was no statistical basis for inviting a comparison as was denoted by the red arrows added to the diagram to show risk reduction, therefore a comparison should not be made in this manner. These modifications gave a visually misleading impression to the reader, distorted as to the significance of the Forest plot, and were in breach of Clause 7.8. In Case AUTH/2168/9/08 the Panel advised both parties of confidence interval overlap and lack of comparator statement and stated that no ruling could be made at that time as it had no complaint on these points. The fact that Novartis had ignored the concerns raised by the Panel contravened the spirit of the Code.

In addition, the published Forest plot showed the patient numbers for every study. This was also reflected in the size of the boxes depicting the relative risk. Thus the size of the studies relative to one another was clear and transparent. In Case AUTH/2168/9/08, the Panel ruled that Novartis had breached Clause 7.8 because it had not reproduced the 'relative risk' boxes in this plot as in the original diagram in the Cochrane review or included the sample size of every study. The adapted Forest plot used in the leavepiece now at issue did not include the sample size of the treatment or control groups from any of the studies. Furthermore, the varying sizes of the boxes on the adapted Forest plot did not accurately reflect the size of the boxes in the original publication, as the box for Zometa was still larger, relative to the other boxes, than in the original paper. In addition, the red colour of the Zometa box gave it undue prominence, relative to the black boxes for all the other medicines. Therefore, Roche believed the immediate impression created by the Forest plot in the leavepiece was misleading in breach of Clause 7.8. The Forest plot also disparaged other companies' products in breach of Clause 8.1. In addition, Novartis' failure to modify the Forest plot according to the ruling in Case AUTH/2168/9/08 was a breach of undertaking in breach of Clause 2.

Roche believed that Novartis had used the Forest plot solely to claim superior efficacy by inviting a comparison of Zometa with the other bisphosphonates. Nowhere had Novartis stated that there were no randomized, controlled, comparative trials as suggested by the Panel in Case AUTH/2168/9/08. The Panel had also acknowledged that the objective of the Cochrane study (Pavlakis *et al*) was to examine bisphosphonates as a class; it was not designed to draw distinctions between any of the medicines studied. This was contrary to the visual impression created and failed to reflect all the available evidence. By using the Forest plot in this manner, Novartis had ignored the Panel and the spirit of the Code.

Roche included the previous Panel judgments below in inter-company dialogue to help Novartis understand its concerns about the leavepiece. It was Roche's intention that it would help to expedite a resolution to this case and thereby avoid protracted dialogue. Novartis considered the judgments irrelevant but did not explain its reasoning.

Case AUTH/869/4/99: the Panel ruled that placement of information from different studies on top of each other invited readers to directly compare the information which was unfair and misleading in breach of Clause 7.2.

Cases AUTH/2061/10/07 and AUTH/2062/10/07 the Panel ruled that the use of secondary endpoints to make a claim in promotional material was misleading and unacceptable.

Roche firmly believed the immediate impression created by the Forest plot, the way in which it had been adapted and the comparisons which it invited were not fair, balanced or based on an up-to-date evaluation of all the evidence. This misled by implication, exaggeration and undue emphasis in breach of Clauses 7.2 and 7.8. Roche also believed the use of these data created confusion between Zometa and other bisphosphonates in the class and disparaged other agents in the class in breach of Clauses 7.2, 7.3, 7.4, and 8.1.

The Panel raised a number of concerns about the use of the adapted Forest plot in Case AUTH/2168/9/08. However, the Panel was unable to make a ruling as a complaint on these specific issues was not made. Roche was concerned as Novartis appeared to have cherry-picked specific excerpts from the Panel ruling and placed undue emphasis on statements which had been taken out of context. Novartis highlighted that, in Case AUTH/2168/9/08, the Panel noted that meta-analysis was an established and valid methodology particularly in the absence of head-to-head trials. However, it was important not to take the Panel's comments out of context, as it went on to state in the following sentence: 'However, the claim was a very strong claim. Readers might expect the supporting data to include randomized, controlled, comparative studies rather than a meta-analysis. There was in the Panel's view a claim for superior efficacy but there had been no complaint in this regard about the exhibition panel'. Although, a breach was not ruled by the Panel on this occasion, Roche believed Novartis had ignored the spirit of the Code by continuing to use the Forest plot from Pavlakis *et al* underneath a slightly modified headline from that ruled on in Case AUTH/2168/9/08.

Roche alleged that, given all of the points raised by the Panel in Case AUTH/2168/9/08, the continued use of the adapted meta-analysis figure from Pavlakis *et al* showed that Novartis had disregarded both the spirit and letter of the Code in a breach of undertaking (as per the Panel's ruling of a breach of Clause 7.8) and as such in breach of Clauses 2 and 9.1.

RESPONSE

Novartis rejected Roche's claim that the heading placed undue emphasis on Zometa's efficacy or led readers to compare the compound's efficacy to that of other bisphosphonates. All studies included in the plot were, as stated in the footnote, either against placebo or no treatment (not 'many' as suggested by Roche.)

The meta-analysis and graph clearly supported the heading that 'Zometa reduces the risk of SREs'. Cochrane collaborations were an independent group, whose publications were highly valued by clinicians and regulatory authorities. The table was not misleading or exaggerated, and was relevant to clinicians treating patients with bone metastases secondary to advanced breast cancer. As such, use of the Forest plot was not a breach of Clause 7.2.

The Panel ruling in Case AUTH/2168/9/08 regarding use of Pavlakis *et al* stated that, 'The Panel noted that meta-analysis was an established and valid methodology particularly in the absence of head-to-head trials'. Novartis chose on this basis to continue to use the Cochrane publications and other independent analyses in its promotional material.

The Panel had, in addition, ruled in Case AUTH/2168/9/08 that an inaccurate 'immediate' impression was created by Novartis using an adaptation of the analysis using the same sized sample size boxes and that this breached Clause 7.8. Novartis subsequently amended the sample size boxes to reflect the sizes referred to in each publication and as originally published. As the Panel had not stated that the sample size needed to be added, Novartis submitted that it had not breached its undertaking. By using proportionately sized sample boxes and including p-values, Novartis believed the adapted Forest plot was no longer misleading and the page contained sufficient information to allow the reader to consider the statistical validity of an individual study. As the reader was only invited to consider the efficacy of Zometa with the heading 'Zometa reduces the risk of SREs', Novartis believed sufficient information was available for the reader to substantiate the heading.

Novartis submitted that every effort had been taken to depict the boxes accurately and the visual inaccuracy in the previous case had not been repeated. The heading for this page in the leavepiece differed from that in the previous case and no claim was made of Zometa's superiority.

Novartis gave due consideration to the previous Panel ruling and the required amendments were made to both the graph and heading. The use of a footnote was at the suggestion of the Panel and demonstrated Novartis's commitment to maintaining the standards of the Code. The graph was accurately labelled and the reader had adequate information to make a judgement on the statistical validity of the results.

Novartis did not believe highlighting Zometa in red breached the Code and furthermore that Roche's references to Panel comments such as 'the confidence intervals for Zometa and pamidronate almost completely overlap' were taken out of context as they specifically addressed the fact that the heading for a claim for superiority in the previous case could not be substantiated when this data was scrutinised.

Novartis therefore denied breaches of Clauses 2, 7.2, 7.3, 7.4, 7.8, 8.1 and 9.1.

With regard to Roche's view that graphs and tables should be faithfully represented, Novartis believed that stylised adaptation was permitted as long as this was not misleading and did not change the meaning. If graphs and tables were to be faithfully reproduced, then any data from black and white journals must be placed in promotional material in black and white. Novartis was concerned of the precedent that this would set for the industry if this were so.

With regard to the previous cases cited by Roche, no clarification of the relevance of these cases to the current case was given. With regard was Case AUTH/869/4/99 the meta-analysis was previously accepted by the Panel as an acceptable use of data in the absence of head-to-head studies, Novartis could not understand the relevance of this case.

Similarly with regard to Cases AUTH/2061/10/07 and AUTH/2062/10/07 as the Pavlakis *et al* meta-analysis did not consider secondary endpoints, Novartis could not understand the relevance to the current case.

Novartis stated that it was incumbent on Roche to explain how and why these previous cases had relevance.

PANEL RULING

The Panel noted that Roche alleged that including data for bisphosphonates other than Zometa beneath the heading 'Zometa reduces the risk or SREs' was a breach of Clause 7.8 of the Code. The Panel noted its ruling in Point 2 above. The Panel considered that the inclusion of data for other products beneath the claim was not unacceptable per se and on the narrow grounds alleged no breach of Clause 7.8 was ruled.

With regard to the modification of the Forest plot, the Panel noted that the version in the leavepiece had a 'Risk Reduction' column added and for each product a percentage figure for the risk reduction was cited in a downward red arrow. The published Forest plot included only the risk ratio (plus 95% confidence intervals). The risk ratios were cited in an untitled column before the column headed 'Risk Reduction'. The Panel considered that the leavepiece did not faithfully reproduce the published Forest plot and the modifications were not made for the purpose of complying with the Code. A breach of Clause 7.8 was ruled. This ruling was not appealed.

The Panel examined its rulings in the previous case.

RELEVANT EXTRACTS FROM THE PANEL RULING IN CASE AUTH/2168/9/08

The Panel noted that the Cochrane review was a meta-analysis of 21 randomised studies which assessed the effect of bisphosphonates, as a class, on skeletal events, bone pain, quality of life and survival in women with early and advanced breast cancer. The primary outcome measure was the number of skeletal events. In nine studies compared with placebo or no bisphosphonates, bisphosphonates reduced SRE risk by 17%. This benefit was most certain with intravenous (iv) pamidronate 90mg, iv zolendronate 4mg and oral clodronate 1600mg. Bisphosphonates in women with advanced breast cancer without clinically evident bone metastases did not reduce skeletal event incidence. The authors' overall conclusion was that in women with advanced breast cancer and clinically evident bone metastases, bisphosphonates reduced the risk of developing skeletal events and skeletal event rate as well as delaying the time to skeletal event.

When discussing implications for clinical practice the authors concluded, *inter alia*, that iv zolendronate (4mg every 3 to 4 weeks) was as effective as iv pamidronate (90mg), with regard to the risk of developing a skeletal event, skeletal morbidity rate, time to a skeletal event, pain and quality of life.

The Panel noted that Roche had alleged breaches of Clauses 7.2, 7.3, 7.4 and 8.1 of the Code in relation to the claim 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer'. The company did not cite any reasons but referred to inter-company correspondence for details of its allegations.

In a letter to Novartis, dated 7 August, Roche gave brief details about why it considered the claim at issue 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast

cancer' was in breach of the Code and referred firstly to the absence of randomised controlled trials comparing the risk of SREs for Zometa vs clodronate or vs Bondronat; and secondly to the fact that the data presented in the Forest plot did not show the risk reduction for SREs for all the medicines and thus did not support the claim.

The Panel noted its concerns about the claim set out below. The Panel also queried whether the exhibition panel made it sufficiently clear that the study was a meta-analysis and there were no randomised controlled trials. The Panel noted that it had no allegation before it on these points. The Panel considered that Roche had made a narrow allegation about the principle of meta-analysis. Novartis had responded accordingly. The Panel noted that meta-analysis was an established and valid methodology particularly in the absence of head-to-head trials. However the claim was a very strong claim. Readers might expect the supporting data to include randomised controlled comparative studies rather than a meta-analysis. There was in the Panel's view a claim for superior efficacy but there had been no complaint in this regard about the exhibition panel. The Panel did not consider that the absence of randomized controlled trials comparing Zometa with clodronate or Bondronat was alone sufficient to render the claim 'Zometa reduces the risk of SREs more than any other bisphosphonate' in breach of Clauses 7.2, 7.3, 7.4 and 8.1 of the Code on the very narrow grounds alleged. No breach was ruled accordingly on this narrow point.

The Panel noted Novartis' submission that the data presented in the Forest plot were for licensed doses lying within each medicines licensed indication. The Panel had concerns about the exhibition panel nonetheless it did not consider that the failure to depict all presentations of medicines examined in the meta-analysis on the Forest plot rendered the claim 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer' misleading, incapable of substantiation or disparaging on the very narrow ground alleged. Only licensed doses were depicted. No breach of Clauses 7.2, 7.3, 7.4 and 8.1 of the Code was ruled accordingly.

The Panel noted that the Forest plot was adapted from one published in the Cochrane Review 2005. The original Forest plot stated the sample size which was also reflected in the varying sizes of the accompanying boxes. Zometa 4mg had the smallest sample treatment size at 114 (control = 113) whilst iv pamidronate had the largest at 367 (treatment) and 384 (control). The exhibition panel did not reflect the sample size. The box for the smallest sample size, Zometa 4mg appeared in red at the top of the Forest plot and was a similar size to the black box for the largest sample size, pamidronate immediately beneath. Whilst p values and confidence intervals were given the Panel, nonetheless, considered the immediate impression created by the Forest plot on the exhibition panel was misleading on this point as alleged; a breach of Clause 7.8 was ruled.

The Panel noted Roche's allegation that the Forest plot compared data from the reduction in risk of SREs for Zometa (an endpoint of events) and the skeletal morbidity rate for ibandronate (an endpoint of time). The Panel noted that the study section 'Data collection and analysis' stated that it relied for the primary outcome measure (number of skeletal events) on the total number of skeletal events reported in each paper. Authors were contacted for additional information that was not in the published trial to permit meta-analysis. The authors noted that the reporting of skeletal events and in particular the rate of events over time varied across the studies. Due to differences in the way outcomes were reported the study reported survival and skeletal event data in two ways: as numbers of events and risk ratios and as ratios of event rates or time to an event. The Cochrane review stated that description and meta-analysis was restricted to those trials from which suitable data could be extracted. The Panel did not consider that the Forest plot was misleading, exaggerated or disparaging as the data was derived from different endpoints as alleged. The Cochrane paper addressed this issue. No breach of Clauses 7.2, 7.3, 7.8, 7.10 and 8.1 was ruled on the narrow point alleged.

The Panel was very concerned about the exhibition panel. The prominent heading in a highlighted red band 'Zometa reduces the risk of SRE's more than any other bisphosphonate in advanced breast cancer' was a strong, unequivocal, comparative claim. It implied that statistically and clinically Zometa was better than the other bisphosphonates listed. The data beneath would be read in light of it. The Forest plot, depicting the overall risk of skeletal events in advanced breast cancer by individual medicine at recommended dosing showed zoledronic acid had the greatest risk reduction at 41%, p=0.001. The data was referenced to the Cochrane review, Pavlakis *et al* (2005) which examined bisphosphonates as a class. It was not designed to draw distinctions between any of the medicines studied contrary to the impression given by the exhibition panel. The Panel noted that whilst the Cochrane study authors commented favourably on individual Zometa studies they did not make a strong unequivocal statement in favour of the comparative efficacy of Zometa as inferred by the heading 'Zometa reduces the risk of SRE's more than any other bisphosphonate in advanced breast cancer' and the data beneath.

The Panel noted that the original Forest plot in the Cochrane review depicted the relative efficacy of each of the available bisphosphonates at their recommended doses compared with placebo or no bisphosphonate. It showed that Zometa achieved the greatest relative risk reduction compared to placebo or no bisphosphonates. Nonetheless the Panel did not consider that the heading was a fair reflection of the study authors' overall conclusions which were more equivocal. In this regard the Panel

noted that the confidence intervals for Zometa and pamidronate almost completely overlapped. Nor did the Forest plot on the exhibition panel make it clear that it depicted the relative risk reduction of each bisphosphonate compared to placebo or no bisphosphonate. It was also unclear where the relative risk reduction of pamidronate at 23% (p=0.00002) depicted on the exhibition panel had come from. The Cochrane review referred to a relative risk reduction of 33%. The position was unclear. The Panel noted however that it had no complaint on these points and thus could make no ruling about them. The Panel considered that the parties should be advised of its views.

Case AUTH/2246/7/09

The Panel considered the Forest plot in the leavepiece at issue in this case was different to the one at issue in Case AUTH/2168/9/08. The heading in the leavepiece 'Zometa reduces the risk of SREs' was different to the exhibition panel previously at issue which stated 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer.'

The leavepiece included some indication of size of the patient population by means of reproducing the size of various boxes used in the original publication. No actual patient numbers were included in the leavepiece although these were given in the published Forest plot.

The Panel noted that in Case AUTH/2168/9/08 the only ruling of a breach regarding the Forest plot was in relation to the narrow allegation that it had been adapted so that all of the studies appeared to contain a similar number of patients in an attempt to mislead the viewer that they all carried the same weight in breach of Clause 7.8. Novartis submitted that this had been addressed by the inclusion of the various sized boxes to reflect the sample sizes. The Panel considered, however, that this change was insufficient as the prominent downward red arrows which depicted risk reduction for each bisphosphonate were all of an equal size. In that regard the Forest plot was misleading with regard to the comparative size of the studies as before and a breach of Clause 7.8 of the Code was ruled. In the Panel's view this represented a breach of the undertaking given in Case AUTH/2168/9/08 and thus a breach of Clause 25 was ruled. Novartis had not maintained a high standard and a breach of Clause 9.1 was ruled. The failure to comply with the undertaking was such that Novartis had brought discredit upon and reduced confidence in the pharmaceutical industry; a breach of Clause 2 was ruled. These rulings were appealed.

The Panel noted Novartis' submission as to how it had changed its promotional material to take account of the previous ruling. The Panel noted, however, that its rulings had to reflect the complainant's allegations and the Panel's lack of comment about an aspect of promotional material did not imply approval. In making its rulings the Panel could also not state precisely how a piece should be changed; it could not, in effect, pre-approve material.

The Panel noted that it had expressed concern about the impression of the exhibition panel in Case AUTH/2168/9/08. In the Panel's view it was clear that although it had only been able to make a ruling on the narrow grounds of the complaint it considered that any claim for superiority for Zometa vs other bisphosphonates, however depicted, could not be substantiated using the Forest plot from Pavlakis *et al*. There had been no allegation in this regard and thus no rulings had been made. Thus in the case now before it, Case AUTH/2246/7/09, there could be no breach of undertaking in this regard and therefore no breach of Clauses 25, 9.1 and 2 was ruled.

The Panel was extremely disappointed that it appeared that Novartis had not taken notice of the Panel's wider comments in Case AUTH/2168/9/08 about the Forest plot. This was disingenuous and unacceptable. The fact that the heading which was a comparative claim had been changed did not in the Panel's view mean that the Forest plot in itself did not imply superiority for Zometa compared to the other bisphosphonates listed. In the Panel's view any graph/diagram etc which incorporated data for a number of medicines would inevitably invite a direct comparison of those medicines. The leavepiece at issue thus visually misled the reader; it invited a direct comparison between the products and implied superiority of Zometa compared with other bisphosphonates. There was no way of knowing if the differences between the products were statistically or clinically significant. Pavlakis *et al* was not designed to draw distinction between any of the medicines contrary to the impression given. The Panel ruled a breach of Clauses 7.2, 7.3, 7.4 and 7.8 of the Code. The Panel considered that the Forest plot as presented in the leavepiece disparaged other companies' products. A breach of Clause 8.1 was ruled. These rulings were not appealed.

APPEAL FROM NOVARTIS

Novartis submitted that it unequivocally respected the Panel's rulings and regarded undertakings and assurances given to the Authority with the utmost seriousness. Novartis had recently improved its processes and increased its resource in order to improve compliance.

Novartis submitted that the Panel's rulings above were heavily dependent on its consideration of its ruling in Case AUTH/2168/9/08. The crucial part of that ruling found that 'The exhibition panel did not reflect the sample size. The box for the smallest sample size, Zometa 4mg appeared in red at the top of the Forest plot and was a similar size to the black box for the largest sample size, pamidronate immediately beneath. Whilst p values and confidence intervals were given the Panel, nonetheless, considered the immediate impression

created by the Forest plot on the exhibition panel was misleading on this point as alleged; a breach of Clause 7.8 was ruled'. The Panel also raised several concerns in Case AUTH/2168/9/08, upon which it could make no rulings as no complaint was made on these points. It did, however, ask that 'the parties should be advised of its views'. In outline, these were that

- The exhibition panel made it insufficiently clear that the study was a meta analysis and there were no randomised controlled trails.

- The heading to the piece did not fairly reflect of the study authors' overall conclusions which were more equivocal.

- The Forest plot did not make it clear that the relative risk reduction of each bisphosphonate was compared to placebo or no bisphosphonate (no treatment).

Novartis submitted that in the light of previous ruling and the undertakings and assurances given by Novartis to the Authority, key changes were made to both the Forest plot and the context in which it was used. Novartis amended the boxes to represent the sample sizes, confidence intervals and risk ratio used in Pavlakis *et al*. The use of different sized boxes to reflect the different sample size and consequent weighting of each study in the meta-analysis reflected conventional statistical methodology.

Novartis submitted that in the current ruling, the Panel had extrapolated from its earlier ruling to conclude that the Forest plot was misleading with regard to the comparative size of the studies because the downward red arrows that depicted risk reduction for each bisphosphonate were equal in size. It was clearly appropriate to represent the boxes according to sample size but it was not appropriate to extrapolate this methodology to the arrows representing risk reduction. The Panel ruled that Novartis had breached its earlier undertaking not to use promotional material similar to the exhibition panel that had been the subject of the ruling in Case AUTH/2168/9/08. However the Panel had stated that the leavepiece was different from the exhibition panel.

Novartis submitted that the Forest plot was a conventional way to represent the results of several studies contributing to a meta-analysis. The size of the box representing the point value for each study was usually made proportional to the contribution of that study to the overall meta-analysis. Thus, the boxes would be smaller for those studies which contained fewer patients and larger for those that contained greater numbers of patients. The size of the box had no significance whatsoever with the regard to the statistical significance of or the conclusions that could be drawn from any particular study. The red arrows used by Novartis in the leavepiece merely represented the point value for the risk ratio derived by Pavlakis *et al* in relation to each study. They were not intended to, and Novartis submitted that it was clear that they did not, represent the pooled data in the meta-analysis. They did not relate to any sample size or weight contribution to the meta-analysis. There was, therefore, no reason why the size of the arrow should be related to the size of the study. The p value was given for each study and it was this that indicated the likely reliability of the value for risk reduction, not the size of the study. It was possible that a more reliable study might contain fewer patients: it might simply be better designed and, thus, more likely to reflect the true difference.

As a consequence of the Panel's advice in Case AUTH/2168/9/08, Novartis also changed its further use of the information contained in the Forest plot (a graphical overview of these changes was provided).

- the heading was changed to 'Zometa reduces the risk of SREs', which was substantiated by the Forest plot underneath it. This was a fair, reasonable and balanced reflection of the authors' conclusions. No comparative claims were made or implied.

- the footnote was changed to 'Adapted from Pavlakis N *et al*, 2005. A review and *meta-analysis* of seven studies involving SREs for breast cancer *versus placebo or no treatment.* Prepared and maintained by the Cochrane Collaboration. Original trials may have had different endpoint' (emphasis added by Novartis). These changes made it clear the study was a meta-analysis and comparisons were made against placebo or no treatment. Novartis noted that, in any event, any of the target audience sufficiently well versed in statistics to derive any useful information from it would immediately recognise the data as representing a meta-analysis since this was by definition the type of study for which a Forest plot was an appropriate way to display the results.

Novartis noted that the red risk reduction arrows on which the ruling of breach of an undertaking was founded were also included on the Forest plot in Case AUTH/2168/9/08. In its ruling in that case the Panel made no comment or recommendation about these arrows. The size of the red arrows was neither the subject of the complaint nor the cause of the previous ruling and therefore should not be the basis of a breach of undertaking. In hindsight Novartis recognised that the inclusion of patient numbers in this graph would have provided greater clarity.

Novartis noted that in Case AUTH/2177/10/08 (Allergan vs Merz) Merz implied that Xeomin was free from complexing proteins and this conferred a clinical advantage which was depicted on a leavepiece with a claim and visual. This was ruled in breach by the Panel.

Merz subsequently produced another leavepiece

with a revised claim used with the (unchanged) visual. The Panel ruled both the claim and the visual separately misleading, as they both individually implied, again, that the fact that Xeomin was free from complexing proteins was a clinical advantage. The Panel also ruled this in breach of undertaking. The Appeal Board on appeal upheld the Panel's ruling that both the claim and the visual were misleading, but did not uphold the ruling of breach of undertaking on the basis that:

- The company had taken steps to comply with the undertaking by modifying the claim
- There had been no previous ruling specifically in relation to the visual

Novartis submitted that the Appeal Board's ruling should act as a precedent in this case which raised similar issues of principle.

Given the changes made to the Forest plot in light of Case AUTH/2168/9/08, Novartis submitted that it had not breached the undertaking and assurance which it gave to the Authority. Thus, as there had been no breach of Clause 25, it could not be said that high standards had not been maintained. Thus, there had been no breach of Clause 9.1 and no breach of Clause 2.

RESPONSE FROM ROCHE

Roche alleged that the Forest plot at issue implied superior efficacy of Zometa by inviting the reader to draw comparisons between the Zometa study and those for the other bisphosphonates. The Zometa data had been highlighted in red. Risk reductions had also been highlighted in red arrows to draw attention to them. The Forest plot had not been faithfully reproduced from the original. It distorted, misled, and did not reflect the intention of the authors of the meta-analysis. Patient numbers had not been included as recommended in the supplementary information for Clause 7.8 and by the Panel. The reworked Forest plot had not taken into account the Panel's opinion in Case AUTH/2168/9/08 and therefore should be considered as a breach of undertaking. The presentation of the Forest plot breached Clauses 2, 7.8, 9.1, and 25.

Roche alleged that Novartis had used the Forest plot by Pavlakis *et al* to claim superior efficacy of Zometa by inviting the reader to draw comparison between Zometa and other bisphosphonates. Novartis had not submitted any representative briefing materials regarding intended detailing of this Forest plot which would help refute this suggestion and have supported its case. A Forest plot was a legitimate way to present data from a meta-analysis, or subgroup analysis in an individual trial. However, this Forest plot had been modified inappropriately from the original to highlight and emphasize Zometa data. It had not been faithfully reproduced with the box and whiskers being different sizes from those in the original. Also the data points and confidence intervals from the Zometa study were highlighted in red in contrast to the other bisphosphonates which appeared in black. The risk reduction column had been added to the Forest plot by Novartis as highlighted red arrows, and the numbers were in a larger font, in contrast to the hazard ratios and p-values. These two creative elements gave particular prominence to certain data favouring Zometa and led the reader to inappropriate comparisons and conclusions regarding the meta-analysis.

The supplementary information to Clause 7.8 recommended inclusion of patient numbers wherever possible. Pavlakis *et al* had included them in its Forest plot but the numbers had been omitted from the leavepiece although their inclusion was suggested by the Panel in Case AUTH/2168/9/08. Novartis had also not stated in the leavepiece that there were no randomized controlled comparative trials as suggested by the Panel in Case AUTH/2168/9/08. The supplementary information for Clause 7 stated that claims in promotional material must be capable of standing alone and should not be qualified by the use of footnotes.

Roche alleged that it was clear from the authors' conclusions that the Cochrane meta-analysis was an attempt to more precisely determine the effect of bisphosphonates as a class on SREs not to draw distinctions between any of the medicines studied. The Panel also acknowledged in Case AUTH/2168/9/08 that the objective of Pavlakis *et al* was to examine bisphosphonate as a class; it was not designed to draw distinctions between any of the medicines studied. This was contrary to the visual impression created by use of the Forest plot in this leavepiece. By continuing to use the Forest plot in this manner, Novartis had not taken into account the Panel's ruling in Case AUTH/2168/9/08 and the spirit of the Code. Roche alleged the presentation of the Forest plot breached Clauses 2, 7.8, 9.1 and 25.

APPEAL BOARD RULING

The Appeal Board noted in Case AUTH/2168/9/08 the Panel had noted that the Forest plot was adapted from one published in the Cochrane Review 2005. The original Forest plot had stated the sample size which was also reflected in the varying sizes of the accompanying boxes. The exhibition panel did not reflect the sample size. The box for the smallest sample size, Zometa 4mg, appeared in red at the top of the Forest plot and was a similar size to the black box for the largest sample size, pamidronate, immediately beneath. Whilst p values and confidence intervals were given, the Panel nonetheless considered the immediate impression created by the Forest plot on the exhibition panel was misleading on this point as alleged; a breach of Clause 7.8 was ruled.

Turning to the current case, Case AUTH/2246/7/09 the Appeal Board noted that the promotional item now at issue was a leavepiece which contained limited information. In the Appeal Board's view, Forest plots were a sophisticated way of presenting

data and some readers would require a degree of explanation before they fully understood the data presented. The Appeal Board noted that in the present case, Case AUTH/2246/7/09, the Forest plot in the leavepiece at issue was different to the one at issue in Case AUTH/2168/9/08. The Appeal Board noted that no actual patient numbers were included in the Forest plot at issue although they were included in the original Forest plot published in the Cochrane Review. Novartis had not appealed the Panel's ruling that the leavepiece did not faithfully reproduce the published Forest plot and the modifications were not made for the purpose of complying with the Code. The Forest plot at issue gave some indication of the size of the patient populations by reproducing the size of various boxes used in the original publication. Some boxes were square and some were diamond shaped. There was nothing in the leavepiece to explain what the different box shapes meant or indeed that the box sizes were proportional to the size of the patient population in the various studies. The Forest plot was misleading with regard to the comparative size of the studies as before. In the Appeal Board's view the use of the downward red arrows depicting the risk reduction added to the misleading representation of the patient populations. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.8. In the Appeal Board's view this represented a breach of the undertaking given in Case AUTH/2168/9/08 and thus it upheld the Panel's ruling of a breach of Clause 25. Novartis had not maintained a high standard and the Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on these points was not successful.

The Appeal Board considered that Novartis had made some effort to comply with its undertaking by making the changes noted above. Thus, in that regard, Novartis had not brought discredit upon and reduced confidence in the pharmaceutical industry as alleged; no breach of Clause 2 was ruled. The appeal on this point was successful.

4 Request for cited references

COMPLAINT

Roche stated that on 13 March 2009, a company pharmacist asked Novartis to email her a copy of the poster, Hoer *et al* (2005), but nothing was received by email or post. After the third request a conference abstract (but not the poster) by Hoer *et al* 2005 was provided on 30 March, twelve working days from the date of the original request. Although Novartis claimed to have posted a response on 19 March this was never received and a copy of that letter had still not been provided. The first time the pharmacist received the actual poster to which the data were referenced was as an attachment to Novartis' inter-company correspondence dated 11 May. Roche alleged that Novartis' failure to supply the references to support the claims made in its leavepiece within ten working days was in clear breach of Clause 7.5.

In addition, on 2 April 2009 the pharmacist emailed a separate request for the Heatley *et al* (2006) poster also referenced in the leavepiece. Novartis supplied an abstract but a second email request, sent on 3 April, which emphasized that the poster was required, was not acknowledged. The first time the referenced poster was provided was as an attachment to the letter from Novartis dated 11 May, over a month after the original request, again in breach of Clause 7.5.

The abstracts did not contain sufficient information to substantiate the claims in the leavepiece. Roche was alarmed at Novartis' inability to provide references to substantiate the data, claims and comparisons. This further affirmed Roche's belief that Novartis did not take its concerns, or the Code, seriously. It was not within the spirit of the Code for Novartis to discriminate in the level of service offered depending on who had requested the information, as suggested in its letters of 11 May and 5 June. Roche noted that the pharmacist as a health professional, was entitled to be provided, within ten working days, with information to substantiate materials, as outlined in Clause 7.5. The signature on all her emails indicated that she was a qualified health professional. This suggested to Roche that the level of service provided by Novartis to health professionals disregarded the requirements of the Code for providing substantiation of information, claims and comparisons and failed to maintain high standards in breach of Clauses 2, 7.5 and 9.1.

As Novartis was unable to provide the Hoer *et al* poster in a timely manner, Roche conducted a literature search for this reference. Although it found the poster it identified a more recent analysis of the Hoer *et al* study published in 2006 with data which differed from that published in the 2005 abstract. The Code stated that, 'Information, claims and comparisons must be based on an up-to-date evaluation of all the evidence'. As the most recent analysis of the Hoer *et al* had not been used in the leavepiece, Roche alleged that the data had been cherry-picked in breach of Clause 7.2.

RESPONSE

Novartis noted that pharmaceutical companies were required to have a scientific services department. It was already common for companies to contact competitors only when they were unable to source cited references eg abstracts, posters, hard to source journals and data-on-file. In this case medical information departments were prepared to respond within the inter-company liaison expectations of ten days rather than response times in Clause 7.5. Therefore Novartis believed that despite citation of this clause by Roche, companies already in principle accepted a slightly differing response expectation than that cited by this clause. This was also clear from the Roche request to the medical information department.

Furthermore Clause 7.5 specifically stated that it

related to requests from 'members of the health professions or appropriate administrative staff'. If this principle was not accepted and Clause 7.5 also applied to competitor companies, then competitors could require all cited references to be supplied regardless of whether they could be easily sourced or not. Thus a pharmaceutical company could easily overwhelm the resources of companies with small medical information departments.

Novartis re-iterated that outside this clause there was still an expectation to provide competitor companies a reasonable response time within the inter-company dialogue rules.

However Novartis re-iterated that customers or health professionals who were treating patients and needed information to make a prescribing decision or consider appropriate use of the medicine must be a priority. These other customers of a medical information department did not have such readily available access to additional resources and would have patients under consideration.

Roche stated Clause 7.5 referred to health professionals who worked for pharmaceutical companies also. Novartis emphasised that this was a very important distinction and that such contact by a health professional was made solely as an employee of the company and not in a professional capacity, in this case as a pharmacist. Again this was a very important distinction as to accept any other interpretation would leave companies who employed individuals who were not health professionals at an unfair disadvantage.

The Hoer *et al* reference was incompletely cited in the leavepiece. Novartis accepted that this was in breach of Clause 7.6. A breach of this clause had not been alleged by Roche. [Novartis had ensured that this referencing error in the leavepiece had been amended.] Roche therefore could not have requested the poster and its communication to Novartis supported this. Consequently, due to a citation error a copy of the abstract was sent on 20 March. This showed that the enquiry was responded to well within ten days. A follow-up to this enquiry flagging non-receipt (30 March) was actioned the same day by email. Evidence to support this sequence of events was provided in confidence only to the Panel - an audit trail of the medical information enquiry from the database.

The Heatley *et al* poster was requested on 3 April, actioned the same day although an abstract was sent in error. Roche contacted Novartis on 7 April to re-iterate that the poster was requested, not the abstract. Novartis accepted that due to confusion at this point this follow-up enquiry was not responded to in a timely manner. In this regard Novartis accepted that it fell short of the standards under which its medical information department operated. Novartis had spoken to the individuals concerned and had reviewed processes to ensure no recurrence. However, whilst this was an unfortunate set of circumstances, Novartis reassured Roche that there was no intention to withhold the information requested.

Novartis rejected Roche's allegation that it had cherry-picked the data. Having found, through a literature search, a 2006 publication of the same study, Roche alleged Novartis was in breach of Clause 7.2, noting that the data differed from that published in 2005. Novartis rejected this as the difference Roche noted was 1% in the percentage of patients on treatment after 6 months of therapy (35% in 2005 vs 36% in 2006). Importantly the 2006 publication also stated a statistically significant risk of patients with a diagnosis of bone metastases not being persistent compared to patients without a diagnosis of bone metastases (p=0.005), which strengthened Novartis' use of Hoer *et al* as a whole to emphasise the issue of oral compliance in metastatic bone disease. The 1% difference did not represent a significant change in the overall conclusions between the 2005 poster and 2006 abstract.

Novartis rejected claims that this represented breaches of Clauses 2, 7.5, and 9.1.

PANEL RULING

The Panel noted that Clause 7.5 required substantiation to be provided as soon as possible and within ten working days at the request of members of the health professions or appropriate administrative staff. There was no exemption for health professionals employed by pharmaceutical companies. The Panel was sympathetic to Novartis' view that its medical information department would prioritise requests from clinicians. Nonetheless, in this instance the request had been for references cited in the leavepiece. In the Panel's view these should have been easily to hand. The Code required substantiation for any information claims or comparisons to be provided within ten working days to any health professional. The Code required substantiation of claims on request and the provision of data on file (Clause 7.7). Clause 7.5 did not require cited references to be provided per se, however the Panel considered that it was helpful to include relevant cited references when asked for substantiation. Additional material could of course be provided. With regard to the provision of Hoer *et al*, there appeared to be a difference between the parties; Roche stated that it had only received the Hoer poster as part of the inter-company dialogue and Novartis stated that the abstract had been sent on 20 and 30 March. According to Novartis, Hoer *et al* (2005) had been incorrectly cited in the leavepiece by omitting to state the material was a poster.

The Panel noted that Novartis had provided the Hoer *et al* abstract to Roche on 30 March. It was not entirely clear from Novartis' records exactly what had been sent. There was no allegation at Point 4 that the abstract failed to substantiate the claims. This would be considered at Point 5 below. Substantiation had been sent by post within ten working days and followed up by email when Roche

contacted Novartis again. It appeared that the copy sent in the post had not been received. In the circumstances the Panel ruled no breach of Clause 7.5.

With regard to the Heatley poster Novartis accepted that this had not been sent. The Panel considered that Roche had, in effect, requested substantiation and thus ruled a breach of Clause 7.5 as substantiation had not been provided in response to a request from a health professional. The Panel did not consider that the failure to supply the Heatley poster meant that high standards had not been maintained. Nor that Novartis had brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clauses 9.1 and 2 was ruled.

The Panel noted the difference between Hoer *et al* (2005) and the 2006 data, this being 1% more patients still on therapy at 6 months ie 36% in 2006 instead of 35% in the 2005 publication. The Panel did not accept that Novartis had cherry-picked the data as alleged. No breach of Clause 7.2 of the Code was ruled.

5 Hoer *et al* reference, claims not substantiated

Page 3 was headed 'There are compliance issues with oral bisphosphonates' followed by a graph headed 'Compliance with oral bisphosphonates' which depicted discontinuation rates at 3 months (44%) and 6 months (65%). The graph was adapted from the poster Hoer *et al* and was a retrospective observation study of health insurance claims.

COMPLAINT

Roche considered the way in which the data from Hoer *et al* were presented misled the reader.

Roche complained to Novartis that the claims referenced to Hoer *et al* were misleading and not substantiated by the abstract supplied by Novartis on 30 March. Novartis provided the poster to Roche during inter-company dialogue. Once Roche had reviewed the full poster it notified Novartis that it strongly believed it was inappropriate to use the data in this manner. The leavepiece was intended for use with health professionals involved in the treatment and management of patients with metastatic bone disease from breast cancer. Hoer *et al* could not substantiate claims about such patients as it comprised a mixed population of men and women with differing diagnoses only 58/497 (11.7%) of which had breast cancer with bone metastases. Evidence suggested that adherence and persistence to oral therapy was better in cancer patients vs patients who had non-oncological chronic disease who, on average, only took half of their prescribed oral medicines. This was thought to be because cancer patients understood the risks, specifically survival, associated with not taking medicines as prescribed (Ruddy *et al* 2009). The use of this reference, without caveats, in the leavepiece was therefore misleading and created confusion.

Furthermore, it was not possible from the data reported in the poster to know which treatments the patients with breast cancer received; and because the persistency rates were not reported by diagnosis it was not clear from the poster or leavepiece what the persistency rate was in the 58 breast cancer patients with metastatic bone disease.

The claims made from this reference were misleading, confusing and not substantiated by the data supplied. Therefore, it was inappropriate to use these data in this manner in breach of Clauses 7.2, 7.3, 7.4, 7.5, and 7.8.

RESPONSE

Novartis responded to points 5 and 6 together and its response is set out below.

Novartis noted that during inter-company dialogue Roche stated in a letter (24 April) that 'As Novartis provided support for the study by Hoer *et al* and one of the authors was a Novartis employee, Novartis should be fully conversant with these data. Therefore, Roche strongly considers use of these data in this manner in promotional materials is inappropriate, fails to maintain high standards and brings discredit to the pharmaceutical industry and as such Roche believes is in breach of Clauses 2, 9.1 and 9.10'. Although dropped from the complaint to the Authority, Novartis strongly believed this kind of misrepresentation of the Code when raising concerns about competitor promotional materials was unreasonable. Novartis strongly believed that in all correspondence there should be a reasonable expectation that the complaint had been fully researched and was appropriate because important resources were used to respond to such complaints.

Novartis considered Roche had misunderstood the relevance of Ruddy *et al* which looked directly at the important issue of oral compliance highlighted in the heading at issue 'There are compliance issues with oral bisphosphonates'. Ruddy *et al* made no mention of bisphosphonates and focused on antineoplastic therapies, but importantly did mention the importance of understanding the issue of compliance in oral therapies, and how this might impact on patient outcomes, and the difficulty in collecting this data, specifically data relating to oncology.

Hoer *et al* presented as a poster and given as a handout at an international conference in 2005 represented a large retrospective observational study from health insurance claims as clearly stated in the footnote under the graph. Novartis did not consider that readers would draw any conclusions other than those presented in the graph, regardless of the actual numbers in the 2005 handout or the 2006 publication. Nor in the company's view would the reader have felt misled having looked at both and drawn conclusions regarding compliance issues with oral bisphosphonates.

The heading set up the representative to discuss the

fact there were compliance issues with oral bisphosphonates as with any oral agent.

Hoer *et al* represented a very large patient number, making its conclusions robust, and specifically presented data for oncology patients rather than the larger patient numbers seen in other publications on persistence with oral bisphosphonates as seen in the post-menopausal osteoporosis setting. Furthermore, this represented a 'real world' compliance data compared with that gathered in prospective randomised controlled trials.

Hoer *et al* looked at all bisphosphonate use based on patients with advanced disease of which the majority of those with metastatic bone disease had breast cancer (53.2%). Despite this study including medicines outside of licensed indication it was most representative of the 'real world' issue of compliance with oral bisphosphonates. Trial data which suggested there were issues related to compliance tended to under report the rate of non-compliance. As there were no randomised controlled trials examining the issue of non-compliance, Novartis maintained this study provided the best representation of potential issues involving the use of oral bisphosphonates. It was well known that bisphosphonates were often inappropriately prescribed out of their licensed indications eg pamidronate or Bondronat in prostate cancer and compliance data in these unlicensed areas was limited.

Greater amounts of compliance data were available for patients taking oral bisphosphonates for post-menopausal osteoporosis, but Novartis considered that only data from the oncology setting should be presented. Novartis maintained that under the heading of oral compliance issues it had used truly representative data to reflect a well recognised issue with oral bisphosphonates in the real world. As such Novartis had acted within the spirit and the letter of the Code and was not in breach of Clauses 7 2, 7.3, and 7.8.

Novartis made no attempt to differentiate around the medicines within Hoer *et al* as all the data suggested it was not just the adverse events, tolerability and benefit outcomes which were important to compliance but also the patient's age, socio-economic factors and the perceived risk-benefit of the medicine especially in chronic disease such as cancer.

Novartis disagreed with Roche's view that because oral Bondronat was not included, the results of the study did not reflect the real world setting in the UK or that it disparaged oral Bondronat. The results were taken from a German population but as Bondronat had approval throughout the European Union in breast cancer it was a therapeutic option in Germany.

As the headings on pages 2 and 3 (facing) of the leavepiece clearly set up what the subsequent graph was representing, Novartis rejected Roche's claims that readers would suppose the bisphosphonates in Pavlakis *et al* were the same as those in Hoer *et al*. There was no attempt in the way this leavepiece was set up to review the information provided on one page and use it to discern something on the other. Roche appeared unnecessarily concerned about this issue in any case as the meta-analysis was not designed for comparison of individual medicines but to show benefit for a class. In the same way page three was not designed to show poor compliance for individual agents but a lowering of compliance rates over time for the class.

No specific compounds were mentioned and this was intentional because compliance issues were recognised as an issue for all oral bisphosphonates. This was supported by the referenced quotations from Heatley *et al*, Conte and Guarneri *et al* (2004) and more recently Aapro *et al* (2008) which were recommended by an international expert panel on bisphosphonate use in solid tumours. Aapro *et al* was sponsored by Novartis but also reviewed and the factual statements and references signed off by all the major manufacturers of bisphosphonates including Roche.

Novartis trusted that the Panel would be satisfied that Novartis was not in breach of the Code as alleged.

PANEL RULING

The Panel examined Hoer *et al* and noted that it was a retrospective observational study using data from health insurance claims. Not all the patients had advanced malignancies involving bone. 109 of the 497 patients had bone metastases. There were a number of limitations listed including that the analysis was limited to the outpatient prescriptions of oral bisphosphonates. The study stated that the risk of being not persistent with therapy was higher for patients with bone metastasis than without such a diagnosis.

The Panel noted that the oral bisphosphonates used were clodronate, alendronate, risedronate, etidronate and/or eidronate and calcium. Of those treatments, only oral clodronate was licensed in the UK for use in cancer patients with bone metastases. The only other oral bisphosphonate so licensed in the UK was Bondronat, marketed by Roche, but this had not been included in the study.

The Panel considered that the heading 'There are compliance issues with oral bisphosphonates' was not unreasonable per se. The Panel considered, however, that given the leavepiece was specifically about patients with metastatic breast cancer the graph would be assumed to apply to the use of bisphosphonates available in the UK for the prevention of SREs in that patient group. The data was not so limited and thus the graph and specific discontinuation claims at 3 and 6 months were misleading and had not been substantiated in that regard. The Panel ruled a breach of Clauses 7.2 and

7.4. The Panel did not consider that the comparison between Zometa (which was administered iv) and oral bisphosphonates was misleading per se and no breach of Clause 7.3 was ruled. The alleged breach of Clause 7.5 regarding the failure to supply Hoer *et al* was dealt with in Point 4 above. The graph did not give a fair and balanced view of the data and thus a breach of Clause 7.8 was ruled.

6 Use of data from Hoer *et al*

COMPLAINT

Roche strongly believed the information from Hoer *et al* presented in the leavepiece was incomplete, ambiguous, misleading, disparaged Bondronat, and included data on medicines not licensed for use in the UK.

The impression created by the page heading above the graph, 'There are compliance issues with oral bisphosphonates' in a leavepiece about Zometa in patients with metastatic bone disease from breast cancer implied the results of Hoer *et al* applied to all oral bisphosphonates prescribed to patients with metastatic bone disease due to breast cancer in the UK. This was compounded by the fact that there were no statements on the page to show which bisphosphonates were studied by Hoer. The study did not include oral Bondronat which accounted for 23% of bisphosphonate usage in UK hospitals, in contrast to oral clodronate which had 3% market share (IMS, Oncology Analyser, September '08) and was included in the study. Clodronate had a different treatment schedule, tablet size, and safety profile from oral Bondronat and so extrapolation of data from one medicine to the other was not justified. Importantly, 39% of the data reported by Hoer *et al* included alendronate which was not licensed for use in metastatic bone disease in the UK.

No information was provided as to the patient characteristics, such as pre-existing comorbidities or which bisphosphonate they received, which might have influenced the outcomes of the study. In addition, no reasons were given for treatment discontinuations, which might have been due to death or to change of therapy. Roche considered the omission of this information and details of which bisphosphonates were used misrepresented the study, was unbalanced, misled and confused readers and prevented them from drawing their own opinion of the validity of the claims made in breach of Clauses 7.2, 7.3, and 7.8.

The impression that the heading 'There are compliance issues with oral bisphosphonates' applied to Bondronat was further emphasized by the Forest plot on the facing page in which the only oral agents shown were Bondronat and clodronate. The overall impression given by these two facing pages was that Hoer *et al* included the same oral bisphosphonates as Pavlakis *et al* and this also encouraged the reader to compare oral bisphosphonates with Zometa.

Roche considered that the heading 'There are compliance issues with oral bisphosphonates', use of Hoer *et al* and the overall impression created when viewed with the Forest plot on the facing page sought to label all oral bisphosphonates as being the same and so were all-embracing, incapable of substantiation, created confusion and misled the reader both by the visual impression given and as to the significance of Hoer *et al*. The title disparaged oral Bondronat, as the market leading oral bisphosphonate, by the overall impression created and the all-embracing claims and was in breach of Clauses 7.2, 7.3, 7.4, 7.8, 7.10, 8.1. Roche strongly considered use of these data in this manner in promotional material was inappropriate, failed to maintain high standards and brought discredit to the pharmaceutical industry in breach of Clauses 2, 9.1 and 9.10.

RESPONSE

Novartis referred to its response at Point 5 above.

PANEL RULING

The Panel noted its comments about Hoer *et al* and its rulings in Point 5 above which covered many of the allegations in Point 6. The Panel considered that the heading in the context of the graph was disparaging and all-embracing. Breaches of Clauses 7.10 and 8.1 were ruled.

The Panel ruled no breach of Clause 9.10. The leavepiece was clearly promotional material and not sponsored material as referred to in Clause 9.10.

The Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 and ruled accordingly.

7 Quotations on page 3

Directly beneath the graph on page 3 were the following three quotations; 'Because IV bisphosphonates are administered in a hospital or infusion centre, compliance with therapy is not a concern' (Heatley *et al*); 'Oral administration requires precautionary measures to ensure absorption and – for some [bisphosphonates] – to avoid gastrointestinal adverse events' (Aapro *et al*) and 'If not taken properly, oral bisphosphonates can cause a high incidence of [gastrointestinal] adverse events, including esophagitis, mucositis, nausea, vomiting and diarrhoea, and may exacerbate this side effects of anticancer therapy' (Conte and Guarneri).

COMPLAINT

Roche believed readers would consider the quotations immediately below the graph from Hoer

et al to be in direct reference to that study. Furthermore, the quotations had been taken out of context and thus were not a true reflection of the individual study outcomes and conclusions thereby constituting cherry picking of data.

The quotation from Heatley *et al* was referenced to a poster which Novartis was unable to provide in response to a request by Roche – only the abstract was sent by Novartis prior to Roche initiating inter-company dialogue, and Roche believed this was in breach of Clause 7.5.

The Heatley abstract appeared to be the result of a literature search to source data on gastrointestinal side effects during oral bisphosphonate therapy. The search only identified one study of breast cancer patients receiving oral bisphosphonate therapy for metastatic bone disease. This was a trial of 55 patients receiving oral clodronate therapy in which the overall compliance was reported to be approximately 90%. A compliance rate of 90% did not reflect or support the claim of 50% non-compliance from Hoer *et al*, as would be expected by the reader, and significantly misled the reader.

Furthermore, Conte and Guarneri listed non-compliance levels with oral Bondronat of 8% and 11-22% for oral clodronate both of which were substantially lower than the 50% non-compliance suggested by the graph.

Finally, Aapro *et al* was produced by an expert panel of clinical oncologists who reviewed the available evidence on the use of bisphosphonates in solid tumours and provided clinical recommendations. Roche alleged that the quotation, 'Oral administration requires precautionary measures to ensure absorption and – for some [bisphosphonates] – to avoid gastrointestinal adverse events', was taken out of context. Particularly as the sentence following it was referenced to a study about compliance of bisphosphonate therapy in patients with osteoporosis rather than metastatic bone disease from breast cancer.

Roche alleged that the quotations and the context in which they were used were misleading as they did not accurately and clearly reflect the slides in question nor the overall meaning of the authors. None of these studies supported the claim that over 44% of patients receiving oral bisphosphonate therapy did not comply with treatment. In fact, they demonstrated 92% complied with oral Bondronat, the most frequently used oral bisphosphonate for the treatment of metastatic bone disease in UK hospitals (IMS, Oncology Analyser, September '08). The quotations were taken out of context, unbalanced, misled as to their overall significance and disparaged oral Bondronat. This was unjustified knocking copy and did not allow the reader to form their own opinion of the therapeutic value of oral bisphosphonates for the treatment of patients with metastatic bone disease and thereby failed to maintain high standards. The use of these quotations was misleading, disparaging and constituted cherry picking of data. Roche alleged breaches of Clauses 7.2, 8.1, and 10.2

RESPONSE

Novartis believed that all the quotations were substantiated by the references cited. As each was appropriately referenced it did not believe that readers would be misled into believing they all referred to Hoer *et al* as suggested. All three explained issues around compliance with oral bisphosphonates and were not taken out of context.

Novartis did not believe the use of the quotations or the context in which they were used misrepresented the authors' publications or that Novartis had cherry-picked the data. Compliance was clearly an important issue for clinicians to consider. Novartis had presented the largest known study of oral agents in the real world metastatic setting. The figures quoted by Roche from Conte and Guarneri simply represented the patient population which withdrew from treatment because of adverse events commonly associated with oral compliance issues. The figures were not specifically a measure of compliance, and so Roche's allegation represented a greater level of cherry picking.

Conte and Guarneri described over 50% non-compliance in osteoporosis suggesting Hoer *et al* was accurate. The authors noted compliance issues might be different from those in a 'real world situation' and this was the data Novartis had used to represent this important clinical issue. Conte and Guarneri also noted that when adverse events could be directly attributable to the medicine, compliance could be even less. The only prospective data in this setting designed to look at compliance came from clodronate studies and there was no trial data to specifically evaluate compliance alone. This, in Novartis' opinion, did not fully represent this issue and was why Hoer *et al* was used.

If Conte and Guarneri was read in full it could be used to support the statement that there were compliance issues with oral bisphosphonates. Hoer *et al* was not unrepresentative of the data in this setting which related to one study with one oral agent. Equally, Novartis denied there was any attempt to link the graph and the referenced quotations as being from the same paper. They were all clearly attributed to different authors, the commonality being concern about oral compliance. As no mention of specific compounds was made, Novartis failed to see how this disparaged Bondronat.

Aapro *et al* was written by the leading oncologists in the field of metastatic bone disease with the lead authors taking part in the registration studies in this setting together with many other international key opinion leaders. Novartis failed to see how the quotation 'Oral administration requires precautionary measures to ensure absorption and - for some [bisphosphonates] – to avoid

gastriointestinal events' had been taken out of context. The paper from which it had been taken was entitled 'Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel' and the quotation appeared under the sub-heading 'choice of administration route'. Although Roche might not be happy with the quotation, it was accurate and taken from an international panel of experts. The reference used to support this statement might not be from the oncology setting which further substantiated the appropriateness of Novartis' earlier use of Hoer *et al*.

Novartis denied breaches of Clauses 7.2, 8.1, and 10.2.

PANEL RULING

The Panel considered that it was clear from the leavepiece that the quotations were from different studies. The Panel did not consider that the readers would assume that the quotations applied to the discontinuation data from Hoer *et al*. In the Panel's view the quotations referred to general issues related to compliance with oral bisphosphonates.

The Panel did not agree that the quotation from Aapro *et al* was out of context given the next sentence referred to its use in oestoporosis. Precautions to ensure absorption of oral bisphosphonates and to avoid gastrointestinal events would apply whatever the diagnosis. Oral Bondronat was to be taken after an overnight fast of at least six hours and before the first food or drink of the day. Fasting had to continue for at least 30 minutes after taking the tablet and patients should not lie down for 60 minutes after taking the tablet.

The Panel did not consider that the quotations disparaged Bondronat. Nor were they misleading or cherry picking the data as alleged. The Panel ruled no breach of Clauses 7.2 and 8.1 of the Code. The quotation was faithfully reproduced and accurately reflected the meaning of the authors. No breach of Clause 10.2 was ruled.

The Panel did not consider that the quotation from Heatley *et al* 'Because IV bisphosphonates are administered in a hospital or infusion centre, compliance with therapy is not a concern' had been taken out of context or was misleading. No breach of Clause 7.2 was ruled. The quotation was clearly about iv bisphosphonates and not linked to the Hoer *et al* data in the graph above it. The Panel did not consider that the quotation was clearly cherry picking of the data as alleged or that it disparaged Bondronat as alleged. No breach of Clause 8.1 was ruled. In the Panel's view the quotation was faithfully reproduced and accurately reflected the meaning of the authors. No breach of Clause 10.2 was ruled. The alleged breach of Clause 7.5 in relation to the Heatley study was considered in Point 4 above.

The Panel similarly considered that the quotation from Conte and Guarneri had not been taken out of context, was not misleading and did not disparage Bondronat. No breach of Clauses 7.2 and 8.1 were ruled. In the Panel's view the quotation accurately reflected the meaning of the authors. No breach of Clause 10.2 was ruled.

Complaint received **6 July 2009**

Case completed **29 October 2009**

MEMBER OF THE PUBLIC v ASTELLAS PHARMA

Conduct of representatives

A member of the public complained that two representatives of Astellas Pharma had sponsored lunch meetings with no educational content. One of the representatives did large stand meetings where she logged a number of GPs with whom she had had no conversation whatsoever.

The detailed response from Astellas is given below.

The Panel noted that the complainant had made a very general allegation. No specific details had been provided. The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities.

The Panel noted Astellas' submission that it had examined all meetings organised since January 2009. It could find no evidence that meetings with no educational content had taken place. The Panel examined the documents generated during the meetings approval process and noted that details of the educational content of each meeting and associated expenditure were given. Since 29 June 2009 all meetings costing less than £100 did not require approval and thus no relevant documents were available. The representatives had denied organising meetings as alleged. The Panel considered that there was no evidence to support the complainant's allegation that the representatives had organised meetings without any educational content. No breach was ruled.

The Panel noted that Astellas had conceded that in contravention of its policy one of the representatives had inflated the number of contacts at exhibition stands by listing all attendees at the meeting rather than those spoken to. The Panel had not seen the relevant Astellas' policy however, Astellas representatives were not incentivised on calls or contact rates. The Panel considered that this was an in-house matter. There was no evidence that representatives had been encouraged or incentivised in relation to contact rates in a way that was contrary to the requirements of the Code. No breach was ruled.

A member of the public complained about the conduct of two representatives of Astellas Pharma Ltd.

COMPLAINT

The complainant stated that to his knowledge the representatives in question had sponsored lunch meetings with no educational content. One of the representatives did large stand meetings where she logged a number of GPs with whom she had had no conversation whatsoever.

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

RESPONSE

Astellas noted that the complainant alleged that the two named medical representatives had sponsored lunches with no educational content and that one of the representatives had falsely logged contacts at 'large stand meetings'. Astellas took the Code very seriously and it had checked its records and interviewed the representatives concerned and could find no evidence to support the allegation that meetings with no educational content had taken place.

With regard to the allegation that one individual had inflated the number of contacts made, while this was an important matter for Astellas to deal with, the company could not see how the Code would apply unless the representatives were incentivised on contact rates. Astellas did not incentivise call or contact rates and therefore it did not consider that the Code applied to such an administrative matter per se. However in the interests of transparency Astellas provided full details of all the stand meetings and the contacts logged by the representatives since 1 January 2009. In summary however Astellas could find no evidence of any Code breaches and in particular no evidence of breaches of Clauses 2, 9.1, 15.2 and 19.1.

Astellas had a thorough, electronic meetings approval process which covered all types of meetings including representative-led audio visual (AV) meetings, Astellas meetings with external speakers and stand meetings (independent NHS-led meetings).

Before 29 June 2009, all meetings (except stand meetings) with external speakers, regardless of cost, were examined by a medically qualified and Code trained individual to ensure an appropriate educational content and level of subsistence, and to check that the speakers had been provided with a written brief and a contract/agreement. These meetings were approved by the regional business manager (RBM) before submission to the medical department. From 29 June 2009 this process was amended as a result of a revised external meetings policy and currently only meetings costing more than £500 were reviewed and approved by the medical department. The RBM would, however, still review and approve all meetings costing more than £100 to ensure Code compliance. Any invitations, speaker briefs and speaker agreements used for these meetings had to be produced on Astellas' pre-

certified templates. AV meetings costing more than £50 (before 29 June 2009) and above £100 (29 June 2009 onwards) also required RBM approval. Stand meetings, regardless of costs, did not require additional medical approval however RBM approval was of course required. This was because Astellas had no input into the agenda or speaker selection.

Astellas had carefully examined all the meetings carried out by the representatives in question since January 2009. The majority of these meetings had been AV meetings where the representative had detailed products to the health professional using a detail aid or a short slide presentation although a few had been incorrectly recorded as AV meetings when they were in fact stand meetings. This was a simple misunderstanding of the term 'AV meeting' and the representative concerned had since correctly differentiated such meetings. However, as Astellas offered no incentives for running any meetings it considered that these mistakes were not directly relevant to the complaint. Subsistence at these meetings had been insignificant sandwiches or snacks. The representatives were interviewed separately and both had denied conducting any meetings without educational content.

A smaller proportion of the meetings had been stand meetings at independent educational events mostly taking place in hospital postgraduate educational centres and occasionally other appropriate locations eg a hotel. The representatives had sponsored such meetings by paying for stand space where they had detailed their products and interacted with health professionals. Four of the meetings examined had involved external speakers paid for by Astellas to discuss a particular disease and its management. In these Astellas-sponsored educational meetings, speakers had received a written speaker brief and had signed a speaker agreement/contract. From the records hospitality had been appropriate to the education provided. Therefore, Astellas had no doubts that the meetings carried out by the representatives, regardless of their type had had an educational content appropriate to the type and duration of the meeting. Hence Astellas submitted that the representatives in question had maintained high standards and had not breached Clauses 2, 9.1, 15.2 and 19.1.

Representatives sponsored independent educational meetings (NHS-led) by paying for stand space. This allowed them the opportunity to detail health professionals on their company's products before and after the meeting and during the session breaks. It would be unusual to be able to speak to every attendee at a large stand meeting but it was also not common practice to have a separate register of attendees at each representative's stand. Commonly a copy was made of the official attendance list, although for small meetings it was likely that representatives who had worked on that territory for many years would know all or nearly all of the attendees to their stands.

Astellas did not incentivise its representatives on the basis of the number of calls or contacts with health professionals. Like most pharmaceutical companies the representatives were incentivised on territory sales obtained from IMS data. There was, therefore, no benefit for representatives to log contacts with health professionals at stand meetings which had not taken place. Although contact with health professionals by representatives was a matter for the Code the recording of such contacts was not covered by the Code unless the representatives were incentivised to breach the Code by company policy. More importantly such mis-recording would be invisible to the external world and would have no impact on health professionals, patients, the NHS or the image of the pharmaceutical industry. Astellas thus believed that such administrative matters should be resolved in-house and were not covered by the Code. If purely administrative issues were indeed covered by the Code, then this would have extraordinary implications for the industry eg would representatives fraudulently claiming expenses become a matter for the Code as well as disciplinary matter?

The contact rate with health professionals by one of the representatives in question was usually above the average for Astellas medical sales representatives and there were several reasons for this. The representative was amongst Astellas' most experienced representatives and had worked on the same territory for approximately 12 years (4 years with Astellas). The individual was therefore well known and also highly regarded by the medical community locally. Understandably over the years the representative had developed a strong professional relationship with health professionals from the region and therefore at stand meetings the interaction and contact with these health professionals might be higher than the average representative.

Notwithstanding this it was clear that the representative had listed all attendees at stand meetings and company policy was that only those health professionals who were actually spoken to should be recorded. However this was a matter for Astellas internally and as stated above there were no benefits whatsoever to inflate contact rates. Additionally Astellas conceded that at large stand meetings it might not be logistically possible to accurately record all contacts and in group conversations there might not always be an appropriate opportunity to ask someone's name before they moved on to another stand. Astellas understood from personal experience in other pharmaceutical companies was that it was normal practice to record all attendees at stand meetings, usually by taking a copy of the attendance register.

Astellas stated that it faced the same dilemma as all pharmaceutical companies in ensuring that contacts logged by a representative had actually been seen by that representative. It was impossible to thoroughly police this but Astellas expected the line

manager to check the meetings records of their subordinates and to scrutinise them against the following rules:

- a person must be spoken to about a product to be counted as a contact;
- a person might be put down as a meeting contact if they were in the audience when key messages regarding promoted products were delivered and
- at stand meetings only those spoken to should be recorded as a contact.

Astellas routinely used agencies to run follow-up interviews with customers to see if the representative delivered the key messages and how they were accepted by the customers. From this Astellas had, on rare occasions, found that the customer had not been called on and it had taken the necessary actions, which on at least one occasion had resulted in dismissal. However it was not easy to perform this validation with stand attendees (contacts) since they might only have had a brief conversation and it was not likely that all messages would have been delivered, making a systematic assessment unreliable.

Astellas did not routinely ask health professionals to sign a register of attendance unless it was an Astellas-sponsored meeting with CPD accreditation. As mentioned above, validation should be the concern of the line manager when approving the meeting expenses.

There was no incentive whatsoever for a representative to list more contacts than actually seen. Astellas did not incentivise representatives for contacts (or calls) made. Astellas' incentives were based on sales results calculated from IMS data.

Astellas did not have incentives or targets for contacts made. However the main reason to put a representative on a territory was to deliver key messages about the company's products to convince the health professional to prescribe them. Therefore it might potentially be of concern if the IMS sales were below expectations and when the number of calls and contacts made on a particular geographical area fell short of historical activity. This was the only potential use of historical call and contact frequency and would be used to probe for an explanation of poor sales performance. However Astellas did not set any targets for such activity and therefore the contact rate would be that which the representative concerned had previously achieved on the territory. There were no issues with sales performance for the representatives in question.

In summary Astellas could find no evidence of any meetings taking place without educational content and Astellas did not incentivise representatives' contact rates and had no policies which might lead to a breach of the Code. Astellas agreed that some contacts had been listed by one representative in error but it did not believe this was a matter for the Code when in these specific circumstances there were no consequences in terms of patient safety, health professionals, the NHS or the reputation of the industry. Astellas denied breaches of Clauses 2, 9.1, 15.2 and 19.1

PANEL RULING

The Panel noted that the complainant had made a very general allegation about the sponsorship of lunchtime meetings which did not have any educational content. No specific details had been provided. The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities.

The Panel noted Astellas' submission that it had examined all meetings organised since January 2009. It could find no evidence that meetings with no educational content had taken place. The Panel examined the documents generated during the meetings approval process and noted that details of the educational content of each meeting and associated expenditure were given. Since 29 June 2009 all meetings costing less than £100 did not require approval and thus no relevant documents were available. The representatives had denied organising meetings as alleged. The Panel considered that there was no evidence to support the complainant's allegation that the representatives had organised meetings without any educational content. No breach of Clauses 15.2 and 19.1 was ruled. Consequently the Panel ruled no breach of Clauses 9.1 and 2.

The Panel noted that Astellas had conceded that in contravention of the company's internal policy one of the representatives had inflated the number of contacts at exhibition stands by listing all attendees at the meeting rather than those spoken to. The Panel had not seen Astellas' policy and procedures on contact rates and visits. The Panel noted the company's submission that representatives were not incentivised on calls or contact rates. The Panel considered that the representative's behaviour on this point was an in-house matter. There was no evidence that representatives had been encouraged or incentivised in relation to contact rates in a way that was contrary to the requirements of the Code. No breach of Clauses 9.1, 15.2, and 2 was ruled.

Complaint received **14 July 2009**

Case completed **3 September 2009**

CASE AUTH/2249/7/09

CONSULTANT UROLOGICAL SURGEON v GLAXOSMITHKLINE

Conduct of representatives

A consultant urological surgeon complained about the conduct of representatives from GlaxoSmithKline promoting Avodart (dutasteride). Previously, before the complainant had researched this himself, he accepted GlaxoSmithKline's claim that there were no comparative studies against the competitor finasteride. This happened again recently. However, there were comparative studies (which showed no advantage for the GlaxoSmithKline product) and indeed could be found through the GlaxoSmithKline website.

The complainant submitted that as this had happened in the past, and he suspected carried on, he believed it was a deliberate marketing strategy.

The detailed response from GlaxoSmithKline is given below.

The Panel noted that in the brief discussion between the complainant and the representative the representative, when asked if there had been any comparative studies between Avodart and finasteride, had stated 'No'. This was not so. In that regard the representative's response was wrong. The representative had not complied with all relevant requirements of the Code and had not maintained a high standard of ethical conduct. Breaches of the Code were ruled as acknowledged by GlaxoSmithKline.

The Panel was concerned that the complainant alleged that representatives had, on other occasions, stated that there were no comparative studies between Avodart and finesteride. No details were given in this regard by the complainant and the previous representative had left the company. The complainant had to establish his case on the balance of probabilities.

The Panel noted that the current Avodart training material referred to finasteride and in particular featured a graph comparing the suppression of dihydrotestosterone by Avodart and finasteride; the Avodart promotional material featured a similar graph. The Panel did not consider that the material encouraged representatives to deny that comparisons between Avodart and finasteride existed. In that regard the briefing material did not advocate a course of action which would be likely to lead to a breach of the Code and no breach was ruled.

A consultant urological surgeon from a general hospital complained about the conduct of representatives from GlaxoSmithKline UK Limited; he named one representative.

COMPLAINT

The complainant explained that he had been visited on a number of occasions by GlaxoSmithKline representatives trying to promote Avodart (dutasteride). Previously, before the complainant had researched this himself, he accepted GlaxoSmithKline's claim that there were no comparative studies against the competitor finasteride. This happened again recently with the representative in question. However, there were comparative studies (which showed no advantage for GlaxoSmithKline product) and indeed could be found through the GlaxoSmithKline website.

The complainant submitted that if it was just one individual one could assume that it was one rogue individual, but as it had happened in the past, and he suspected carried on, he now believed that this was a deliberate marketing strategy and amounted to lying. The complainant thought this was supposed to have been stopped after previous GlaxoSmithKline problems with anti-depressants.

When writing to GlaxoSmithKline the Authority asked it to respond in relation to the requirements of Clauses 7.2, 7.3, 15.2 and 15.9 of the Code.

RESPONSE

GlaxoSmithKline submitted that having investigated the complaint it accepted, and sincerely regretted, that the complainant was indeed misled by one of its representatives. The company accepted breaches of Clauses 7.2 and 15.2 of the Code.

However, GlaxoSmithKline firmly believed that the breaches which occurred were due to an error made by an individual representative and did not reflect any aspect of GlaxoSmithKline's marketing strategy. Specifically, GlaxoSmithKline did not accept that any of the comparisons between Avodart and finasteride made in its promotional materials contravened either Clause 7.2 or 7.3. GlaxoSmithKline also submitted that its representatives were provided with sufficient training (both in terms of seminar style teaching sessions and written briefing materials) to enable them to effectively promote Avodart without breaching the Code (Clause 15.9). Therefore Clauses 7.3 and 15.9 had not been breached.

Interaction between the representative and the complainant

GlaxoSmithKline submitted that the

representative's written account of his interaction with the complainant was as follows:

'I had an appointment to see the complainant after clinic.

The conversation followed as below –
***R** (representative), C (complainant).*

***R** - I am [name] the new urology representative from GSK. Can I start by asking if you have ever prescribed Avodart and in which patients?*

***C** - I have never prescribed Avodart and only use finasteride as there is no benefit of Avodart over finasteride and it is also cheaper.*

***R** - That is interesting. Please can I take a few minutes to show you some data to demonstrate the benefits of Avodart?*

***C** - Have there been any comparative studies between finasteride and Avodart?*

***R** - No, there have not....(C interrupted)*

***C** - There have been and I have seen them on your own SmithKline website and they showed no difference between the two. You have lied so please leave.*

***R** - Thank you for your time.*

I stood up and left the room.'

GlaxoSmithKline acknowledged that the representative's response to the complainant's question was incorrect; as the complainant noted, there had been a number of head-to-head studies comparing Avodart with finasteride.

When interviewed by his line manager, the representative clearly knew that there were a number of studies directly comparing Avodart and finasteride and accepted that his answer was incorrect. The representative stated that he felt flustered by being asked such a direct question right at the start of his meeting and that he gave an immediate incorrect answer under pressure rather than taking a moment to compose a more considered response. Before the representative had time to qualify his response he was asked to leave. Sales material which the representative had with him at the time and intended to talk through with the complainant included comparisons between Avodart and finasteride.

Abstracts pertaining to GlaxoSmithKline's sponsored studies were publicly available via gsk.com. There were nine abstracts on the website relating to head-to-head studies of Avodart and finasteride.

A number of studies which compared Avodart with finasteride were used in GlaxoSmithKline's promotional and training materials.

GlaxoSmithKline expected Avodart representatives to be fully conversant with these studies.

Promotional material available to Avodart representatives

GlaxoSmithKline provided all the relevant promotional materials available to Avodart representatives where a comparison between Avodart and finasteride was made. Within this material Avodart was compared to finasteride in three specific contexts:

Isoenzyme inhibition: GlaxoSmithKline claimed that finasteride was a selective inhibitor of the type 2 5α-reductase (5AR) isoenzyme whilst Avodart inhibited type 1 and type 2 5AR isoenzymes (Bartsch *et al* 2000 and Andriole *et al* 2004).

Dihydrotestosterone (DHT) suppression: A direct comparison between Avodart and finasteride was made relating to their effect in terms of suppressing levels of the androgen DHT. This claim was supported by a randomised controlled trial which compared the effects of Avodart and finasteride at their licensed doses in terms of DHT suppression (Clark *et al* 2007).

Retrospective efficacy study: The benign prostatic hyperplasia (BPH) cost model (provided) used a retrospective study which compared the clinical efficacy of Avodart and finasteride (Issa *et al* 2007). The nature of this study was clearly explained within the cost model.

Training and briefing materials provided to Avodart representatives

Before representatives were permitted to promote any product they must have:
- completed an initial generic two week in-house training programme covering topics such as the GlaxoSmithKline sales model, medical information resource and safety reporting, ethical requirements and the Code and NHS structures;
- completed a two week Avodart specific initial training programme (ITP) and
- passed an in-house examination to assess familiarity with the Code and passed an in-house examination to confirm satisfactory completion of the ITP.

As required by Clause 16.3, all representatives had to take and pass the ABPI Medical Representatives Examination within the prescribed time limit.

The representative in question joined GlaxoSmithKline in 2005 and promoted various GlaxoSmithKline products. Following successful completion of the Avodart ITP he started to promote Avodart in June 2009.

GlaxoSmithKline confirmed that the representative had:
- passed the ABPI representatives examination;
- completed an initial GlaxoSmithKline generic

training program in 2005;
- passed the internal ITP examination in June 2009 and
- completed the Avodart specific ITP course in June 2009.

GlaxoSmithKline advised that the Avodart ITP comprised the training manual, a 2 week ITP course and the ITP examination. The detailed training manual was circulated as pre-reading prior to the ITP course. The manual covered the male urogenital system, BPH and its diagnosis, treatment of BPH and the profile for dutasteride. The contents page relating to each module and those pages from within the manual which covered studies comparing Avodart to finasteride were provided.

The two week ITP course itself included sessions on a variety of clinical and non-clinical topics. Clinical sessions were delivered by members of the GlaxoSmithKline medical department with experience in the field of urology. Non-clinical sessions were mainly led by members of the Avodart marketing team. Training sessions were delivered in an interactive seminar style and used pre-approved PowerPoint presentations. Within the clinical sessions, studies comparing Avodart and finasteride were covered a number of times. The training slides which referred to such studies were provided. Non-clinical topics included an introduction to the Avodart marketing strategy, which was covered in some detail, and familiarisation with the available promotional material. Representatives were taken through presentations explaining how an interview with a health professional should be structured around the relevant detail aid. These presentations were provided. At no point during their training were representatives encouraged, explicitly or implicitly, to withhold information from health professionals with regard to those trials which directly compared Avodart with finasteride.

The written ITP multiple choice examination tested the candidate's understanding of the clinical data and marketing strategy which was covered on the course.

Action to mitigate the risk of similar breaches occurring in the future

GlaxoSmithKline submitted that on 24 July 2009 the representative in question was required to spend half a day with his line manager. During this session it was made clear that his actions had resulted in a breach of the Code. The representative clearly understood the seriousness of this issue and the fact that breaches of the Code might result in disciplinary action. The discussion moved on to cover the reasons why this breach occurred and consider how the representative could avoid making a similar error in the future. The representative was also required to spend half a day with a member of the GSK medical department; the agenda included:
- a review of all instances where trials comparing Avodart with finasteride were covered within the approved training materials;
- a review of currently available promotional materials focussing on those items where Avodart and finasteride were compared and
- an opportunity to practice, in a role-play setting, handling various questions health practitioners might raise regarding comparisons between Avodart and finasteride.

GlaxoSmithKline also considered it important to remind all other Avodart representatives of the key studies comparing Avodart with finasteride. At the next scheduled training event in September 2009, a member of the GlaxoSmithKline medical department would prepare an interactive teaching session covering all the key studies which had compared these two products.

Conclusion

GlaxoSmithKline accepted that the unfortunate actions of a single representative had resulted in breaches of Clauses 7.2 and 15.2. However, it was confident that the accuracy of its promotional material and the adequacy of the training given to its representatives before they were permitted to promote Avodart meant neither Clause 7.3 nor Clause 15.9 had been breached.

The complainant referred to previous interactions with Avodart representatives. The region in which the complainant worked was without an Avodart representative between July 2008 and July 2009. The previous representative no longer worked for GlaxoSmithKline so the company had not been able to investigate the element of the complaint which related to past activity. However, results from the key trials comparing Avodart with finasteride had been available for a number of years and GlaxoSmithKline was confident that Avodart representatives had been adequately briefed since the product was first promoted in the UK in 2003.

GlaxoSmithKline remained committed to the ethical promotion of its medicines and aimed, at all times, to comply with both the letter and the spirit of the Code.

PANEL RULING

The Panel noted that in the brief discussion between the complainant and the representative the representative, when asked if there had been any comparative studies between Avodart and finasteride, had stated 'No'. This was not so. In that regard the representative's response was wrong and so the Panel ruled a breach of Clause 7.2. The representative had not complied with all relevant requirements of the Code and had not maintained a high standard of ethical conduct. A breach of Clause 15.2 was ruled. GlaxoSmithKline had acknowledged these breaches of the Code.

The Panel was concerned that the complainant alleged that representatives had, on other

occasions, stated that there were no comparative studies between Avodart and finesteride. No details were given in this regard by the complainant and the previous representative had left the company. The complainant had to establish his case on the balance of probabilities.

The Panel noted that the current Avodart training material referred to finasteride and in particular featured a graph comparing the suppression of dihydrotestosterone by Avodart and finasteride; the Avodart promotional material featured a similar graph. The Panel did not consider that the material encouraged representatives to deny that comparisons between Avodart and finasteride existed. In that regard the briefing material did not advocate a course of action which would be likely to lead to a breach of the Code. No breach of Clause 15.9 was ruled.

Complaint received **15 July 2009**

Case completed **8 September 2009**

CASE AUTH/2250/7/09

VOLUNTARY ADMISSION BY GLAXOSMITHKLINE

Travel health proposal to a local buying group

GlaxoSmithKline voluntarily admitted that it had inadvertently breached the Code in relation to a pricing proposal, written by a member of its travel health sales force, and provided to a local buying group. The Authority's Constitution and Procedure provided that the Director shall treat an admission as a complaint if, *inter alia*, it related to a potentially serious breach of the Code. Failing to certify material was a serious matter and the admission was accordingly treated as a complaint.

In March 2009 a member of a local buying group (a practice manager) asked its travel health representative for pricing information. The representative asked to present to the group but, given the timescales, this was not possible; the information was asked for in written form within two days.

The representative agreed with her regional business manager that she would compile the information. The regional business manager reviewed and approved the document. Three hard copies, together with an approved promotional item were given to the practice manager who asked for an electronic copy which was circulated to other members of the group.

In May 2009 the representative received a similar request from a different buying group and provided it with the same material, omitting only the listed names of members of the other buying group. No other practices had received this information nor had any other representatives sent similar information.

Although the material was produced as a pricing proposal, GlaxoSmithKline took the view that the claim 'Excellent Products' made this a promotional item. GlaxoSmithKline therefore believed it was in breach of the Code as the claim 'Excellent Products' was used, without qualification or substantiation; prescribing information, non-proprietary names and the statement on adverse event reporting were all omitted; neither the representative nor her manager recognised the material as a promotional item requiring submission for Code certification, they had misunderstood the Code and GlaxoSmithKline's procedures, which clearly stated that such material should be approved by head office. Therefore they had failed to maintain a high standard and despite this being contrary to their instructions, GlaxoSmithKline took full responsibility for this inappropriate conduct. The nurse audit referred to in the proposal was a medical service provided by GlaxoSmithKline. Its aim was to facilitate identification of patients for a booster injection where necessary. The non-promotional service was open to all UK practices. However, the service was referred to within this promotional material in breach of the Code.

GlaxoSmithKline took any breaches of the Code and matters of misconduct very seriously. The individuals concerned had passed their ABPI examination and there was clearly no wilful intent to contravene the Code. This was the only incident of this nature that had occurred with these two individuals. GlaxoSmithKline had maintained high standards in relation to format, suitability and taste of the material and its processes and standard operating procedures were adequate and clear and this incident did not reflect a failure in these processes. Due to the isolated nature of this incident and the corrective actions, which were outlined below, GlaxoSmithKline firmly believed that it had not brought discredit upon or reduced confidence in the industry.

GlaxoSmithKline stated that all recipients of the proposal had been told that the material was inappropriate. GlaxoSmithKline had requested that the material be destroyed or electronic copies deleted. The representative and her manager were retrained on all processes and would receive specific Code retraining. The travel health team would receive additional Code training to that regularly provided within the company.

GlaxoSmithKline deeply regretted this situation had occurred based on one piece of material with limited distribution by one person.

The detailed response from GlaxoSmithKline is given below.

The Panel noted that the travel health proposal included three sections outlining how GlaxoSmithKline Travel Health could help practices by providing 'Excellent Products', practice support services and competitive prices. The document had been provided in response to a request for pricing information. The document described GlaxoSmithKline's products as, *inter alia*, 'Excellent'. As the document contained a claim for the products it had to be considered to be promotional and could not take the benefit of the exemptions to the definition of promotion. The representative had provided another buying group with similar material.

With regard to the proposal provided to the buying group in March 2009 the Panel considered that, in the context in which it appeared, 'Excellent' implied some special merit for GlaxoSmithKline's products which was misleading. Breaches of the Code were ruled as acknowledged by GlaxoSmithKline.

The Panel noted that the document did not contain prescribing information, there were no non-proprietary names next to the most prominent display of the brand names nor was there an adverse event reporting statement. Breaches of the Code were ruled as acknowledged by GlaxoSmithKline.

The Panel considered that the representative and her manager had not maintained a high standard of ethical conduct. The document had not been certified. Breaches of the Code were ruled.

The promotional document referred to a non-promotional nurse audit which was offered as a medical service by GlaxoSmithKline. A breach of the Code was ruled as acknowledged by GlaxoSmithKline.

The Panel noted that GlaxoSmithKline had admitted a breach in that the Code required companies to be responsible for the activities of their representatives if these were within the scope of their employment even if they were acting contrary to the instructions which they had been given. The Panel considered that GlaxoSmithKline had demonstrated that it had taken responsibility for the representative and her manager.

In the Panel's view, creation of unapproved promotional material by the field force was of serious concern. High standards had not been maintained and a breach of the Code was ruled. Nonetheless, the Panel considered that the material before it was not such as to bring discredit upon or reduce confidence in the pharmaceutical industry. Clause 2 of the Code was used as a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

GlaxoSmithKline UK Ltd voluntarily admitted that it had inadvertently breached the Code; the matter was brought to GlaxoSmithKline's attention on 10 June 2009 by a competitor company and related to a pricing proposal, written by a member of its travel health sales force, and provided to a local buying group. As soon as GlaxoSmithKline knew about the material it conducted a full and comprehensive investigation to establish how such a breach occurred and what corrective actions needed to be taken.

The action to be taken by the Authority in relation to a voluntary admission by a company was set out in Paragraph 5.4 of the Constitution and Procedure which stated, *inter alia*, that the Director shall treat the matter as a complaint if it related to a potentially serious breach of the Code. Failing to certify material was a serious matter and the Director decided that the admission should be treated as a complaint.

COMPLAINT

GlaxoSmithKline stated that in March 2009 a member of a local buying group (a practice manager) asked its travel health representative for pricing information. The representative asked for the opportunity to present the information to the group but, given the timescales to which the buying group was committed, this was not possible; the information was asked for in written form within two days.

The representative agreed with her regional business manager that she would compile the information and submit it to him for review. The regional business manager duly reviewed and approved the use of the document. Three hard copies were given in a folder, together with an approved promotional item, to the practice manager representing the buying group. The practice manager asked for an electronic copy of the pricing proposal and it appeared that this was then circulated to other members of the group.

In May 2009 the representative received a similar request from a separate buying group and provided it with the same material, omitting only the listed names of members of the other buying group.

No other practices had received this information nor had any other representatives sent similar information.

Although the material was produced as a pricing proposal, GlaxoSmithKline took the strict view that the claim 'Excellent Products' made this a promotional item in breach of the Code as follows:

- The claim 'Excellent Products' was used, without qualification or substantiation, in breach of Clauses 7.2 and 7.10.
- Prescribing information, non-proprietary names and the statement on adverse event reporting were all omitted, in breach of Clauses 4.1, 4.3 and 4.10 respectively.
- Neither the representative nor her manager recognised the material as a promotional item requiring submission for Code certification so Clause 14.1 was also breached.
- The representative and her manager had misunderstood the Code and GlaxoSmithKline's procedures, which clearly stated that such material should be approved by head office. Therefore they had failed to maintain a high standard in the discharge of their duties, and despite this being contrary to their instructions, GlaxoSmithKline took full responsibility for this inappropriate conduct. Clauses 15.2 and 15.10 had therefore been breached.
- The ITHENA Nurse Audit was a medical service provided by GlaxoSmithKline, under Clause 18. The aim of this service was to facilitate identification of patients for a booster injection where necessary. The non-promotional service was open to all UK practices. However, the service was referred to within this promotional material in breach of Clause 18.4.

GlaxoSmithKline took any breaches of the Code and matters of misconduct very seriously and this

incident was of particular concern given the extensive Code, procedural and general training its representatives received. Both the individuals concerned had passed their ABPI examination. Following a comprehensive review of the circumstances that had led to this breach, there was clearly no wilful intent to contravene the Code, in letter or in spirit, by either of the individuals involved. This was the only incident of this nature that had occurred with these two individuals. The investigation revealed that this was an isolated case, and there was no suggestion that other members of the field force similarly misunderstood the requirements. GlaxoSmithKline's intention had always been to comply with the Code. GlaxoSmithKline had maintained high standards in relation to format, suitability and taste of the material and its processes and standard operating procedures were adequate and clear and this incident did not reflect a failure in these processes. Due to the isolated nature of this incident and the corrective actions, which were outlined below, GlaxoSmithKline firmly believed that it had not brought discredit upon or reduced confidence in the industry, therefore it had not breached Clause 2.

GlaxoSmithKline stated that those involved with this case had expressed deep remorse that their failure to understand the Code's requirements had led to this breach of the Code.

GlaxoSmithKline had undertaken that:

- All recipients of the proposal had been contacted and told that the material was inappropriate. GlaxoSmithKline had requested that the material be destroyed or electronic copies deleted.
- The representative and her manager were retrained on all processes and would receive specific Code retraining. Both had received short term objectives, as part of the GlaxoSmithKline disciplinary process, to ensure that they fully understood the Code.
- The travel health team including both sales and marketing departments, would receive additional Code training this year to that regularly provided within the company.

GlaxoSmithKline deeply regretted this situation had occurred based on one piece of material with limited distribution by one person. GlaxoSmithKline stressed its commitment to maintaining high standards in all its activities.

When writing to GlaxoSmithKline to inform it that the matter would be taken up under the Code, the Authority asked the company to consider the requirements of Clause 9.1 in addition to those it had already cited.

RESPONSE

GlaxoSmithKline reiterated that it had voluntarily notified the Authority of breaches of the Code in respect of Clauses 4.1, 4.3, 4.10, 7.2, 7.10, 14.1, 15.2, 15.10 and 18.4.

The proposal at issue was produced by one of the travel health representatives in response to a request for information from a member of the local buying group.

GlaxoSmithKline took any breaches of the Code and matters of misconduct very seriously and this incident was of particular concern given the extensive Code, procedural and general training its representatives and account managers received. GlaxoSmithKline also acknowledged that the use of uncertified material was a potentially serious issue. Therefore the company had written to the two local buying groups concerned to request that all copies of the proposal were destroyed or deleted. At no time had patient safety been impacted.

As soon as GlaxoSmithKline knew about the material it conducted a full and comprehensive investigation, to establish how such a breach occurred, and what appropriate corrective actions needed to be taken. The sequence of events was outlined above. Although they did not breach the Code intentionally, the two employees involved were going through a formal disciplinary procedure.

GlaxoSmithKline had supported the ITHENA audit nurse team in order to facilitate best practice regarding completion of travel vaccination schedules. The service was available to all practices so that they might ensure that patients who had not completed their course of vaccination against hepatitis A, hepatitis B and/or typhoid, might be recalled to complete the course as appropriate. Provision of the service was not dependent on the prescribing of GlaxoSmithKline's vaccines and the briefing document enclosed made this clear.

GlaxoSmithKline noted that it had been specifically asked to comment on Clause 9.1. While it acknowledged that the document in question technically became promotional material by virtue of the inclusion of the claim 'Excellent Products', the proposal otherwise explained the discounts and services available to the local buying group in accordance with Clause 18.1. The group received the information it was seeking within the short timelines set. GlaxoSmithKline was committed to maintaining high standards through training of its employees and establishing a culture of ethical conduct. GlaxoSmithKline had taken this isolated incident seriously by putting those involved through a disciplinary procedure. GlaxoSmithKline therefore believed that Clause 9.1 was not breached, as the information requested by the buying group was provided in a timely and appropriate manner and it had acted to maintain the high standards expected of it. Both the representative and the regional business manager had passed their ABPI Medical Representative's Examination.

GlaxoSmithKline was committed to and took pride in maintaining high standards. Appropriate action had been taken and the company trusted that it had demonstrated that it had recognised that this was a very serious matter which it would ensure would not happen again.

PANEL RULING

The Panel noted that the Travel Health Proposal included three sections outlining how GlaxoSmithKline Travel Health could help practices by providing 'Excellent Products', practice support services and competitive prices. The document had been provided in response to a request for pricing information. The document described GlaxoSmithKline's products as, *inter alia*, 'Excellent'. As the document contained a claim for the products it had to be considered to be promotional and could not take the benefit of the exemptions to the definition of promotion in Clause 1.2. The representative had provided another buying group with similar material.

With regard to the proposal provided to the buying group in March 2009 the Panel considered that, in the context in which it appeared, that 'Excellent' implied some special merit for GlaxoSmithKline's products which was misleading. Breaches of Clauses 7.2 and 7.10 were ruled as acknowledged by GlaxoSmithKline.

The Panel noted that the document did not contain prescribing information for those products referred to, there were no non-proprietary names next to the most prominent display of the brand names nor was there an adverse event reporting statement. Breaches of Clauses 4.1, 4.3 and 4.10 respectively were ruled as acknowledged by GlaxoSmithKline.

The document had not been certified. A breach of Clause 14.1 was ruled.

The Panel considered that the representative and her manager had not maintained a high standard of ethical conduct. A breach of Clause 15.2 was ruled.

The promotional document referred to a non-promotional nurse audit which was offered as a medical service by GlaxoSmithKline. The supplementary information to Clause 18.4, Provision of Medical and Educational Goods and Services, stated that printed material designed for use in relation to the provision of such goods and services must be non-promotional. A breach of Clause 18.4 was ruled as acknowledged by GlaxoSmithKline.

The Panel noted that GlaxoSmithKline had admitted a breach of Clause 15.10. Clause 15.10 required companies to be responsible for the activities of their representatives if these were within the scope of their employment even if they were acting contrary to the instructions which they had been given. The Panel considered that GlaxoSmithKline had demonstrated that it had taken responsibility for the representative and her manager. No breach of Clause 15.10 was ruled. [Post meeting note: Clause 15.10 is an explanatory Clause and is not capable of infringement].

In the Panel's view, creation of unapproved promotional material by the field force was of serious concern. High standards had not been maintained and a breach of Clause 9.1 was ruled. Nonetheless, the Panel considered that the material before it was not such as to bring discredit upon or reduce confidence in the pharmaceutical industry. Clause 2 of the Code was used as a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

Complaint received **14 July 2009**

Case completed **24 August 2009**

HEALTH PROFESSIONAL v CEPHALON

Promotion of Effentora

A health professional complained that a Cephalon representative had clearly promoted the sublingual use of Effentora (buccal fentanyl citrate).

Effentora was indicated for the treatment of breakthrough pain in adults with cancer who were already receiving maintenance opioid therapy for chronic cancer pain. The tablets were to be placed in the upper portion of the buccal cavity.

The complainant noted that according to the summary of product characteristics (SPC) Effentora was not licensed for sublingual use. The complainant was concerned that representatives had promoted this 'off licence' use and that inaccurate information had been given to health professionals which could potentially lead to patients being treated on inaccurate data.

In response to a request for further information, the complainant stated that two different representatives had made the claim and that other physicians within the local primary care trust had also heard it.

The detailed response from Cephalon is given below.

The Panel noted that the complainant's identity had not been revealed to Cephalon although the company had been told which PCT he worked in.

The Panel considered that it was impossible to know who had said what to the complainant about sublingual Effentora or whether such information had been given in response to an unsolicited request. The complainant had stated that two different representatives had mentioned that Effentora could be used sublingually. The complainant had also referred to other colleagues within the PCT being told about sublingual use of Effentora although no corroborating evidence was provided in this regard. A judgement had to made on the available evidence and the balance of probability bearing in mind that extreme dissatisfaction was usually required on the part of an individual before he or she was moved to complain.

Darwish *et al* (2009) reported that sublingual use of a fentanyl buccal tablet was a viable alternative to buccal placement in patients who might require an alternative administration site. On 25 February 2009 Cephalon's medical department emailed the sales marketing management to state that Darwish *et al* was outside the product licence and so must not be discussed with customers. Requests from health professionals for information about the study could be forwarded to medical information or to the medical scientific liaison team. The sales representatives were only briefed verbally to forward enquiries to medical information. In the Panel's view it was inadequate to only verbally brief representatives on an off-label issue that was likely to generate interest. No details of that briefing were supplied. In July, after it had received this complaint, Cephalon had written to its staff reminding them that sublingual use of Effentora was outwith the licence and that requests for information on such use should be referred to medical information.

The Panel was also concerned that from Cephalon's response a medical scientific liaison executive might have both a non promotional role ie responding to unsolicited enquiries, and what could be a promotional role ie presenting on technical issues that were beyond the scope of the sales representative. This might have added to the confusion.

The Effentora promotional material referred only to buccal use. An in-house presentation about the Code, used at the Effentora launch meeting, clearly stated that requests for off-label information would be dealt with by the medical information department.

The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. The Panel was concerned that, in the first instance, representatives had only been verbally briefed about the sublingual use of Effentora. Nonetheless the training at the Effentora launch meeting clearly explained how off-label queries should be handled. Representatives should have been well aware that sublingual administration of Effentora was outwith the licence. The Panel did not consider that the complainant had provided evidence to show that, on the balance of probabilities, either a representative or a member of the medical scientific liaison team had promoted the sublingual use of Effentora. The Effentora briefing material did not advocate sublingual use. No breach of the Code was ruled.

A health professional complained about the promotion of Effentora (buccal fentanyl citrate) by Cephalon (UK) Limited.

Effentora was indicated for the treatment of breakthrough pain in adults with cancer who were already receiving maintenance opioid therapy for chronic cancer pain. The tablets were to be placed in the upper portion of the buccal cavity.

COMPLAINT

The complainant stated that a Cephalon representative had told him that Effentora could be administered sublingually. The representative was very clear in their promotion of this mode of administration as a benefit of the product. The complainant checked the Effentora summary of product characteristics (SPC) and, in fact, this was an unlicensed mode of administration. The complainant was concerned that representatives had promoted this off licence use having spoken to a number of local fellow clinicians. The complainant was also concerned that Cephalon had given inaccurate information to health professionals when prescribing decisions on these products were being made which could potentially lead to patients being treated on inaccurate data.

When writing to Cephalon, the Authority asked it to respond in relation to Clauses 3.2, 15.2 and 15.9 of the Code.

RESPONSE

Cephalon submitted that the sales representatives had only been briefed on the buccal use and administration of Effentora. No briefings had suggested that other routes of administration were appropriate.

Cephalon submitted that if health professionals referred to a published pharmacokinetic study assessing the bioequivalence of sublingual and buccal fentanyl buccal tablet (Darwish *et al* 2009), sales representatives were verbally briefed to forward any enquiries to medical information. This study was only available from Cephalon via an unsolicited request forwarded to medical information. An email sent on 25 February 2009 to the marketing sales management, emphasised this following publication of the paper.

Cephalon submitted that the complainant referred to a specific representative visit and the alleged off licence use also being promoted locally. Cephalon submitted that the representative who covered the complainant's area could only recollect a question being asked about sublingual delivery of Effentora, in response to which the enquiry was referred to medical information and a member of the medical scientific liaison team. A discussion of this information was then initiated by the health professional, to which the representative concerned stated he was unable to discuss this topic and any further points should be referred to medical information.

Cephalon submitted that its sales representatives received Code update training which included specific reference to promotion within the scope of the SPC.

Cephalon refuted the alleged breaches of Clause 3.2, 15.2 and 15.9. A specific briefing had been sent to the sales teams to remind them of the requirement to forward any requests for information on sublingual (and any other information that fell outside the scope of the SPC) to medical information.

FURTHER COMMENTS FROM CEPHALON

In response to a request for further information, Cephalon explained that its medical scientific liaison team was a field-based extension of its medical affairs medical information function. The team reported to the medical director and responded to unsolicited enquiries from health professionals about detailed technical points or aspects that fell outside the marketing authorization. Furthermore, the team might receive requests from health professionals for presentations to clinical teams on technical details that went beyond the scope of the sales representatives. The team also trained clinical teams participating in a phase IV clinical trial, working in partnership with the clinical research organisation managing the trial. This involved education on breakthrough cancer pain, the administration of the fentanyl buccal tablet and dose titration. The job description for the function, which formed the basis of the role briefing, was provided. Two of the three appointees were from medical information/medical affairs backgrounds, and were familiar with the requirements of the Code for such roles. The third came from a clinical science role via sales and had received additional training and coaching.

It was possible that the complainant had seen a member of the medical scientific liaison team. However, the team would have only discussed sublingual Effentora if the health professional had made a specific and unsolicited request for the information, or following a referral from a sales representative who was unable to address the request. It was difficult to verify whether someone from the team saw the complainant in view of their being anonymised for the purposes of the complaint.

Cephalon stated that health professionals might have referred to Darwish *et al*, hence enquiries arising about sublingual use.

The sales representatives were briefed as to how to comply with the Code if asked about any situation that was outside the marketing authorization during the Effentora launch meeting. Several scenarios were provided, and the need to forward any enquires to medical information relating to off-licence use was emphasised verbally.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that the claim was mentioned to him by two different representatives (he could not remember their level/seniority) and that other physicians within the local primary care trust (PCT) had told him that they had also heard the claim.

PANEL RULING

The Panel noted that the complainant's identity had not been revealed to Cephalon although the company had been told which PCT he worked in.

The Panel considered that it was impossible to know who had said what to the complainant about sublingual Effentora or whether such information had been given in response to an unsolicited request. The complainant had stated that two different representatives had mentioned that Effentora could be used sublingually. The complainant had also referred to other colleagues within the PCT being told about sublingual use of Effentora although no corroborating evidence was provided in this regard. A judgement had to made on the available evidence and the balance of probability bearing in mind that extreme dissatisfaction was usually required on the part of an individual before he or she was moved to complain.

The Panel noted that Darwish *et al* reported that sublingual use of a fentanyl buccal tablet was a viable alternative to buccal placement in patients who might require an alternative administration site. Effentora was indicated only for buccal placement. On 25 February 2009 an email was sent from Cephalon's Medical Department to the sales marketing management which stated that Darwish *et al* was outside the product licence and so must not be discussed with customers. Requests from health professionals for information about the study could be forwarded to medical information or to the medical scientific liaison team who could address the query. The sales representatives were only briefed verbally to forward enquiries to medical information. In the Panel's view it was inadequate to only verbally brief representatives on an off-label issue that was likely to generate prescriber interest. No details of that briefing were supplied. In July, after it had received this complaint, Cephalon sent a written briefing document to its staff reminding them that sublingual use of Effentora was outwith the licence and that requests for information on such use should be referred to medical information.

The Panel was also concerned that from Cephalon's response a medical scientific liaison executive might have two roles, a non promotional role ie responding to unsolicited enquiries, and what could be a promotional role ie presenting on technical issues that were beyond the scope of the sales representative. This might have added to the confusion.

The Panel noted that the Effentora promotional material supplied by Cephalon referred only to the buccal use of the medicine. An in-house presentation about the Code, used at the Effentora launch meeting, clearly stated that requests for off-label information would be dealt with by the medical information department.

The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. The Panel was concerned that, in the first instance, representatives had only been verbally briefed about the sublingual use of Effentora. Nonetheless the training on the Code delivered at the Effentora launch meeting clearly explained how off-label queries should be handled. Representatives should have been well aware that sublingual administration of Effentora was outwith the licence. The Panel did not consider that the complainant had provided evidence to show that, on the balance of probabilities, either a representative or a member of the medical scientific liaison team had promoted the sublingual use of Effentora. No breaches of Clauses 3.2 and 15.2 were ruled. The Effentora briefing material did not advocate sublingual use. No breach of Clause 15.9 was ruled.

Complaint received **20 July 2009**

Case completed **16 October 2009**

CASE AUTH/2252/7/09

PROFESSOR v CV THERAPEUTICS

Conduct of representative

A hospital professor complained that a sales representative from CV Therapeutics Europe (recently acquired by Gilead Sciences Europe) had tried to use the offer of a memory stick as an inducement to gain an interview with him.

The complainant stated that he had completed a card in connection with Ranexa (ranolazine) which offered him a memory stick. The representative in question, accompanied by an unknown colleague, arrived without an appointment and asked to see the complainant. The complainant's secretary told the representative that the complainant was busy but that he would be grateful if information about ranolazine, together with the memory stick was left. The representative left product information but refused to leave the memory stick without seeing the complainant.

The detailed response from Gilead is given below.

The Panel noted that the parties' accounts differed: it was extremely difficult to know exactly what had transpired. A judgement had to be made on the available evidence and the balance of probability, bearing in mind that extreme dissatisfaction was usually required on the part of an individual before he or she was moved to complain.

According to the complainant the representative had asked to see him in relation to the completion of the reply paid card. Both the complainant's PA and secretary had spoken to the representative. The complainant's secretary had told the representative that the complainant was busy and requested that the information about ranolazine and the memory stick be left. The representative had clearly stated that she would not leave the memory stick without seeing the complainant. The complainant stated that he had not crossed the box on the reply paid card asking the representative to call.

According to Gilead, when advised by the complainant's PA that the complainant did not have to see the representative, the representative replied along the lines of 'I know and I will get one to you'. Gilead acknowledged that the failure to provide the memory stick at the first visit could have been perceived as only providing it in return for a call. The representative had only called on the complainant because he had requested information. The representative had the information in her bag but in error did not have the memory stick.

The Panel considered that it was most unfortunate that the representative had not had the memory stick with her at the initial call. Particularly as the representative was calling in conjunction with the reply paid card completed by the complainant. The fact that the representative did not have a memory stick with her at the initial call was not in itself necessarily a breach of the Code. However, the impression given was important; a clear and unambiguous explanation should have been given.

According to Gilead a memory stick had been left later that day for the complainant; this had not reached the complainant. Both parties agreed that one had been sent by post. The Panel noted Gilead's submission that representative had made every effort after the brief meeting with the complainant's secretary to ensure the complainant received a memory stick and to rectify her error. The Panel noted the parties did not agree on the content of the conversation between the representative, the complainant's PA and the secretary. It appeared that the representative had not clearly explained the situation. The Panel was concerned that there did not appear to be any specific comment from the representative's line manager regarding what had happened at the first visit to the centre.

The Panel considered that the representative's failure to deliver the requested memory stick and the information at the same time together with the fact that the complainant was unable to see the representative might have given the impression that the memory stick was being used as an inducement to gain an interview. This poor impression was compounded by the fact that according to the information before the Panel the representative did not clearly state that she had inadvertently left the memory stick in her car and that she would deliver it later that day. Taking all the circumstances into account the Panel considered that the representative had in effect, albeit in part due to her error in leaving the memory stick in the car, given the impression that it was being used an inducement to gain an interview as acknowledged by Gilead and a breach of the Code was ruled.

It was not possible to determine precisely what had been said. On the basis of the parties' submissions the Panel did not consider that, on balance, there was sufficient evidence to show that on the balance of probabilities the representative had failed to maintain a high standard of ethical conduct. The impression given by failing to leave the memory stick at the outset was covered by the ruling of a breach of the Code above. Both parties agreed that, at the very least, a memory stick had been sent by post the following day. The Panel

ruled no breach of the Code. This ruling was appealed.

The Appeal Board noted the further evidence submitted by each party. Differences in the parties' accounts remained. A judgement had to be made on the balance of probabilities.

The Appeal Board considered that it was most unfortunate that the representative had not had the memory stick with her at the initial call. The Appeal Board was also very concerned that at the appeal hearing the representative's line manager stated that he had not heard of what was said between the representative and the complainant's PA during the first visit to the centre, despite being in close proximity to the parties.

The Appeal Board noted from the representative that later in the day she had tried unsuccessfully to telephone the hospital centre where the complainant worked. Unable to make telephone contact (due to a wrong number) the representative stated that she had then returned to the centre with a memory stick from her car. The representative could not recall how she had entered the centre however it was most likely that another person was using the door or the door was open. The representative stated that the reception was deserted so she left the memory stick together with a post-it note on the inside of the reception screen. The representative stated that she had not gone further into the centre as she considered that this would have made her an uninvited visitor. The Appeal Board noted that the complainant had stated that it was not possible to enter the reception when it was unmanned without ringing a bell and being let in. In any event the memory stick had not reached the complainant.

The Appeal Board noted from the representative that she had accessed her voicemail at 1.55pm but had not received a voicemail left by the complainant's PA (asking her to return to leave a memory stick) until 4pm, when she was on her way home. According to the representative this delay was apparently not unusual and was due to pockets of poor mobile telephone reception. On her return to home the representative had posted a further memory stick to the complainant together with the reply card, a note and her business card. The representative had not thought to include in her note that she had already left a memory stick at the centre.

The Appeal Board noted that both parties agreed that, at the very least, when the representative first visited the centre she had not got a memory stick with her but one had subsequently been sent by post and received by the complainant. It was not possible to determine precisely what had been said or taken place in the intervening time. There was a direct conflict of evidence. On the basis of the parties' submissions the Appeal Board did not consider that the complainant had satisfied the burden of proving that, on the balance of probabilities, the representative had failed to maintain a high standard of ethical conduct. The Appeal Board upheld the Panel's ruling of no breach of the Code. The appeal was not successful.

A hospital professor complained about the conduct of a contact sales representative working for CV Therapeutics Europe Ltd. CV Therapeutics had recently been acquired by Gilead Sciences Europe Ltd.

COMPLAINT

The complainant noted that he had previously completed a card in connection with Ranexa (ranolazine) which offered him a memory stick. On Friday, 17 July, the representative in question, accompanied by a male colleague, arrived at the complainant's hospital centre without an appointment and asked to see him in connection with the completion of this card. The complainant's secretary told the representative that the complainant was busy but that he would be grateful if she left some information about ranolazine, together with the memory stick. The representative left information about the product but refused to leave the memory stick without seeing the complainant. This appeared to be a clear breach of Clause 15.3 regarding the use of inducement or subterfuge to obtain an appointment with a medical practitioner.

When writing to CV Therapeutics Europe the Authority asked it to respond in relation to the requirements of Clauses 15.2 and 15.3.

RESPONSE

Gilead responded to the complaint and stated that both it and the contract company recognised their responsibilities with regard to the conduct of representatives and took any alleged breach of the Code very seriously. There had been a full investigation. Unfortunately there were few facts available and Gilead was limited to the representative's recollection of the day.

Gilead submitted that the complainant had completed a reply paid card which offered a memory stick and had asked for more information on Ranexa. The representative in question had a lunchtime meeting arranged in another department in the hospital on 17 July. She took this opportunity to call on the complainant before her other meeting but the receptionist told her that he was unavailable. The representative left some information on Ranexa but did not leave a memory stick as she should have done. The representative had admitted that she did not have the memory stick with her at the time as she had not checked her bag before the call. However, after her other meeting, somewhere between 2.30 – 3pm, the representative returned to the hospital centre to rectify this. Unfortunately the reception counter was unmanned so the representative left a memory stick on the counter with a note attached as to who it should go to.

The complainant's secretary had also called the representative after her initial visit and left a message on her telephone. The representative only listened to this message at about 4pm later that day after she had left the site. As she assumed that the complainant had not got the first memory stick she posted a second one to him. Gilead did not know if the complainant had received either of these memory sticks.

Gilead submitted that there was never any intention of only providing a memory stick in return for a call, although the representative recognised that her failure to provide the stick at the first visit could have been perceived in that way. She took appropriate action to ensure that she rectified her error by returning to the unit later the same day, and also by posting a memory stick after a call from the complainant's secretary. Gilead therefore denied a breach of Clause 15.3.

Gilead submitted that the representative had passed the ABPI Medical Representatives Examination and had worked in the industry for a number of years. She was a well regarded member of the contract team with a good record. Although Gilead could not verify her version of events, it had no reason to doubt her. The representative recognised that she made a mistake by not having a memory stick available at the first visit, but made every effort to rectify this. In this regard, she had maintained a high ethical standard of conduct and therefore had not breached Clause 15.2.

Gilead hoped that this explained the circumstances that led to the complaint. Gilead accepted that the representative's mistake could have led to the perception that the memory stick would only be given if the doctor accepted an appointment, but believed that her subsequent actions on the same day demonstrated that this was not the case.

FURTHER COMMENTS FROM THE COMPLAINANT

In response to a request for his comments on the above, the complainant stated that the secretary who initially spoke to the representative (and who had dealt with this correspondence), his PA and he were shocked at Gilead's response because it was untrue. The complainant noted that the representative arrived in his department accompanied by a male colleague.

The complainant explained that he and his PA were based upstairs in the hospital centre; the PA went down to speak to the representative and explained that the complainant would be grateful if she would leave some information. When asked if she could leave the memory stick the representative clearly stated that she would not leave it without seeing the complainant; there was no suggestion that she did not have a memory stick with her. The representative told the complainant's secretary that she had a meeting on site and left Ranexa literature together with her business card which included her mobile telephone details. When the complainant heard the representative's response, he asked his secretary to telephone her with the message that it was not acceptable for her to say that she would only leave the memory stick if the complainant saw her and that she should return to leave the memory stick. No response was received to this message which was left around lunchtime.

The complainant stated that the representative could not have returned to the hospital centre and found the reception counter unmanned; if reception was unmanned then the doors into the centre were locked. Furthermore it was not possible that the representative left a memory stick on the counter with a note attached because it would have been passed on to the complainant; the department in which he worked was small and secure, there was no question that the memory stick could vanish into thin air. Furthermore if the representative did not have a memory stick with her in the first instance how did she manage to produce one without apparently leaving the hospital site?

The complainant stated that when he submitted the complaint (Monday, 20 July) he had heard nothing from the representative but on Tuesday, 21 July he received a memory stick that had been posted on Saturday, 18 July. The memory stick was in a small box and attached to the original card which he had completed. The card stated 'please send me: a USB memory stick containing further information about Ranexa' and the complainant had crossed this box. There was another box on the card regarding a Ranexa representative call which the complainant had not crossed. Attached to this card was the representative's business card which stated 'Apologies! Please find enclosed the memory stick'. There was no suggestion on this card that she had previously left a memory stick. The complainant presumed that if she had left a stick in his department she would have attached his card to this rather than to the one that was posted.

The complainant wished to raise the issue about representatives trying to insist on appointments with doctors to hand over things such as memory sticks. He was disappointed therefore that it had now been compounded by the representative's dishonesty which would seem to be a more serious issue than the one he originally raised! The complainant was also disappointed that the representative's version of events had in effect cast doubt on both what his PA reported and the reception staff who did not leave the department unmanned with the door open.

FURTHER COMMENTS FROM GILEAD

Gilead explained that the representative was accompanied by her line manager who had arrived at the hospital to support her; the representative had two lunchtime meetings booked. Afterwards the representative and her manager spent time in the hospital following up on leads generated from the meetings. They finished at around 2 – 2.30pm. The line manager was with the representative when

she visited the complainant's hospital centre on the first occasion.

The representative would not ordinarily have called on the complainant if she had not received a reply paid card. The representative had visited the complainant because he had requested information. It was a speculative call; the representative expected to just leave the information but wanted to give the complainant the option of an appointment. The representative had not heard of the hospital centre where the complainant worked and wanted to know more about it. Neither the representative nor her manager had visited the centre before.

The representative and her manager recalled the centre as an annex outside of the main hub of the hospital and not easy to find. They recalled a reception area, with a sliding window in the wall on the left hand side. A receptionist was on the other side of the window. The representative asked at the window if she could see the complainant. The receptionist called the complainant's PA who came down the stairs. The representative walked to the foot of the stairs to talk to the PA.

The whole interaction with the PA lasted just a few minutes. The representatives asked to make an appointment or to see the complainant. The PA said no, as the complainant was in a meeting until lunchtime. The representative offered to call back (she was on her way to lunchtime meetings elsewhere in the hospital) but the PA said no, the complainant did not want to see her. By this time the representative had read the notice board and it appeared that the centre was more about another disease rather than cardiology. The representative said to the PA that she was not sure that Ranexa was of interest to the complainant, however she would leave the literature and if it was of interest to him he could call her. The representative therefore left her business card.

The representative looked in her bag for the literature, which would have included the product monograph and the memory stick, which broadly contained the same information as in the product monograph; it could also include a selection of other literature and a leavepiece. At this point the representative realised that she did not have the memory stick. The PA saw the representative was looking for one, and said something like 'he does not have to see you to get a stick'. The representative replied along the line of 'I know that and I will get one to you'. The representative believed that the PA thought she would not go back with the memory stick.

The representative left the centre to attend her lunchtime meetings and switched her telephone off for the meetings. The representative returned to her car at around 2.30pm and found a data stick with her other materials in the boot of the car. It was still raining heavily and the representative was keen to start her drive home. The representative tried several times to call the hospital centre reception to ask if she could post the memory stick on (to avoid walking back through the rain). When the representative was unable to get through, she walked back over to the centre and took the stick with her.

The representative was clear that she was able to access the centre through the main door. The representative cannot recall anyone in the vicinity and she could see no-one on the other side of the sliding window. The representative left the stick just inside the sliding window. This whole process took only a couple of minutes. The representative did not enter the hospital centre and therefore this was not inconsistent with the fact that the centre was locked when the reception desk was unmanned.

The representative arrived home around 6pm (a journey of around 3.5 hours) and she picked up a telephone message from the complainant's secretary at about 4pm regarding the memory stick. By this time the representative had left one at the hospital centre. However, within 10 minutes of getting home the representative wrote her apologies to the complainant on the reply paid card and posted it, together with a second memory stick. The representative recognised that she should have had a memory stick in her bag at the first visit however she acted to rectify her error.

Gilead submitted that it could find no evidence to support the complainant's allegation that the representative's version of events was untrue. In particular, it was now clear that the representative could have entered the hospital centre reception when it was unmanned and left the memory stick as she stated. The representative did not claim to have entered the centre itself which, as the complainant stated, would not have been possible.

As such, Gilead did not believe that the representative's actions were in breach of Clauses 15.2 or 15.3. While the representative was wrong to have not had the memory stick with her at the first visit, she made very effort to rectify this and at no time intended only to provide the memory stick only if an appointment was granted.

PANEL RULING

The Panel noted that the parties' accounts differed: it was extremely difficult in such cases to know exactly what had transpired. A judgement had to be made on the available evidence and the balance of probability, bearing in mind that extreme dissatisfaction was usually required on the part of an individual before he or she was moved to complain.

According to the complainant the representative had asked to see him in relation to the completion of the reply paid card. Both the complainant's PA and secretary had spoken to the representative. The complainant's secretary had told the representative that the complainant was busy and requested that the information about ranolazine and the memory

stick be left. The representative had clearly stated that she would not leave the memory stick without seeing the complainant. The complainant stated that he had not crossed the box on the reply paid card asking the representative to call.

According to Gilead, when advised by the complainant's PA that the complainant did not have to see the representative, the representative replied along the lines of 'I know and I will get one to you'. Gilead acknowledged that the failure to provide the memory stick at the first visit could have been perceived as only providing it in return for a call. The representative had only called on the complainant because he had requested information. The representative had the information in her bag but in error did not have the memory stick.

The Panel noted that Clause 15.3 stated that representatives must not employ any inducement or subterfuge to gain an interview. No fee should be paid or offered by a representative for the grant of an interview.

The Panel considered that it was most unfortunate that the representative had not had the memory stick with her at the initial call. Particularly as the complainant had completed the reply paid card and the representative was calling in conjunction with that reply paid card. The fact that the representative did not have a memory stick with her at the initial call was not in itself necessarily a breach of the Code. However, the impression given was important; a clear and unambiguous explanation should have been given.

According to Gilead a memory stick had been left later that day for the complainant; this had not reached the complainant. Both parties agreed that one had been sent by post. The Panel noted Gilead's submission that representative had made every effort after the brief meeting with the complainant's secretary to ensure the complainant received a memory stick and to rectify her error. The Panel noted the parties did not agree on the content of the conversation between the representative, the complainant's PA and the secretary. It appeared that the representative had not clearly explained the situation. The Panel was concerned that there did not appear to be any specific comment from the representative's line manager regarding what had happened at the first visit to the centre.

The Panel considered that the representative's failure to deliver the requested memory stick and the information at the same time together with the fact that the complainant was unable to see the representative might have given the impression that the memory stick was being used as an inducement to gain an interview. This poor impression was unacceptable and was compounded by the fact that according to the information before the Panel, the representative did not clearly state that she had inadvertently left the memory stick in her car at the hospital and she would deliver it after her lunchtime meetings. Taking all the circumstances into account the Panel considered that the representative had in effect, albeit in part due to her error in leaving the memory stick in the car, given the impression that it was being used an inducement to gain an interview as acknowledged by Gilead and a breach of Clause 15.3 was ruled.

It was not possible to determine precisely what had been said. On the basis of the parties' submissions the Panel did not consider that, on balance, there was sufficient evidence to show that on the balance of probabilities the representative had failed to maintain a high standard of ethical conduct. The impression given by failing to leave the memory stick at the outset was covered by the ruling of a breach of Clause 15.3 above. Both parties agreed that, at the very least, a memory stick had been sent by post the following day. The Panel ruled no breach of Clause 15.2. This ruling was appealed.

APPEAL FROM THE COMPLAINANT

The complainant alleged that the representative's account of events was untrue and so he appealed the ruling of a breach of Clause 15.2. If her account was to be believed, then someone within his own department had taken the memory stick that she claimed to have delivered.

The complainant noted that the representative described the interaction with his PA who she claimed said that the complainant did not want to see her. The complainant stated that this was not the case, since the representative (and her line manager) arrived without an appointment but his PA stated that it would not be possible that day. The representative also claimed that she realised that she did not have the memory stick and that his PA then said something like 'he does not have to see you to get a stick'. This was untrue as it was not until the complainant's PA returned and spoke to him later, and told him what had happened, that he explained to her that it was not necessary for him to see the representative to get the memory stick. As a result, the complainant then asked his PA to telephone the representative, whom they understood was still in the hospital at other meetings, to make the point that he did not need to see her to receive the memory stick and could she return and leave the memory stick in addition to the product literature that she had already left.

The complainant noted that the representative claimed that after she had attended her lunchtime meeting in another part of the hospital she had tried several times to call the hospital centre reception but was unable to get through. The complainant submitted that this was unlikely since there were five lines but in any case there was an automatic answering service which took messages but no message was left.

The representative stated that she was clear that she was 'able to access the centre through the main door'. The complainant noted that this was correct but from a photograph of the building (provided),

this meant that she could not actually enter the centre at all. When no-one was at the desk in the entrance area, the outside door was locked and it was necessary to press the bell and wait for this to be opened. It was therefore impossible for the representative to have entered the building and leave the memory stick where she stated. Once someone was inside the building, there were no locked doors whatsoever and the representative would have easily been able to enter the main part of the centre and have spoken to other members of staff who would have been around. The complainant particularly resented the fact that the representative had suggested that she left a memory stick just inside the sliding window. Clearly, if she had done this and the complainant did not receive it, it implied that one of the staff must have taken the stick and not passed it on to him.

The complainant noted that the representative, once home, had posted a memory stick to him which he subsequently received on Tuesday after he had already written to the Authority. The complainant enclosed a copy of what the representative had sent him. The memory stick was attached to the card he had originally completed, as was a business card from the representative. Surely if the representative had left a memory stick within the department as she claimed, she would have already left the card which representatives normally brought with them when they followed up on one of these responses? On a note the representative had written on her business card she apologised but did not mention that she had already left a memory stick within the department.

The complainant noted Gilead's submission that it could find no evidence to support his allegation that the representative's version of events was untrue. Gilead then stated that in particular, it was now clear that the representative could have entered the hospital centre reception when it was unmanned and left the memory stick as she stated. The representative did not claim to have entered the centre itself, which as Gilead stated, would not have been possible. Clearly, from its comments Gilead failed to understand the nature of the centre and the fact that the representative could not have entered any part of the centre and that if she had entered any part of the centre, she then could have entered the whole of the department as there were no other locks. The complainant therefore alleged that the representative's actions and Gilead's response to his complaint were clearly in breach of Clause 15.2 of the Code.

COMMENTS FROM GILEAD

Gilead submitted that having carefully considered the appeal it could find no new evidence presented, rather it reiterated the complainant's previous comments. Gilead and the contract company had thoroughly investigated the complaint and had separately interviewed both the representative and her manager. Gilead had challenged their statements in the light of the responses from the complainant. Throughout the process, their statements had been consistent.

Gilead submitted that the difficulty in cases such as these was that there was little hard fact on which to base an opinion. Much of what was being considered was the recollections of two people, particularly with reference to the conversation between the complainant's PA and the representative. Similarly, the representative claimed that after her meeting and left a memory stick on the reception desk; the complainant argued that it was impossible to do this as the door to the centre was always locked if the reception was unmanned. Again, with no witnesses to the event, Gilead was unable to ascertain fact.

In view of the above, Gilead and the contract company had sought evidence to refute or corroborate the representative's statement. Looking at the sequence of events, there was no dispute that the complainant had completed the reply paid card requesting information on Ranexa and a memory stick. Both parties agreed that the representative called upon the unit accompanied by her manager.

The differences in opinion regarding the conversation between the representative and the complainant's PA were difficult to assess, but it appeared that there was agreement that the representative had made clear that she was remaining in the hospital for other meetings, the complainant had stated that he then asked his PA to telephone the representative whom they understood was still in the hospital at other meetings. The representative's claims that she tried to call the hospital centre were confirmed by her itemised telephone bill which showed that she called the centre three times although at a time slightly earlier than she stated. The representative did not leave a message as she hoped to speak to the complainant or his PA to ask if she could post the memory stick due to the heavy rain, therefore she called the hospital switchboard to see if she could be transferred to the complainant directly on two further occasions. This was clearly documented in the itemised telephone bill (provided).

Gilead submitted that the representative then claimed to have returned to the centre, found the reception unmanned, and left a memory stick with a note. The complainant claimed that this would be impossible as the door would have been locked if reception was unmanned. With no witness or other evidence, it was impossible to determine the exact course of events. Even if there was a rule within the centre that the door should be locked if reception was unmanned, could the complainant be certain that on the day, at the time the representative stated that she returned, the receptionist had not left her desk for a few minutes and left the door open?

Gilead agreed that the PA left a voicemail message for the representative who, on retrieving it later that day, posted a second memory stick to the

complainant and included the reply paid card. This was on the evening of 16 July [sic], which meant that the collection would be the following day. This was consistent with the complainant's statement that he received the memory stick on the Tuesday.

As previously stated, there were limited facts available in this case. However, all of the facts available were consistent with the representative's statement and, indeed, the complainant's.

Gilead had accepted that the representative's failure to deliver the memory stick on the first visit gave the impression that it was being used as an inducement to gain an interview in breach of Clause 15.3.

While Gilead had made every effort to establish exactly what happened on the day in question, there remained much which was based on personal recollection. However, all of the facts available supported the representative's position. Thus Gilead agreed with the Panel's ruling of no breach of Clause 15.2.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant was astonished that Gilead claimed that no new evidence had been presented in his appeal and that it was a reiteration of his previous comments. The complainant noted that he had provided photographic evidence that showed the door which was kept shut was on the outside of the building and he was confident that this would be the case if the secretary was not there. The bell was then rung and it rang in other offices within the building and someone would then let the person in. If indeed, the representative had got into the building despite this, then no other doors within the building were locked and it would have been quite easy for her to enter another office and find someone to speak to.

The complainant noted that representatives usually brought a card like the one that he completed when they followed up with a visit. Gilead had not tried to answer the question of what happened to the memory stick and note that was supposedly left in the reception area. The complainant would have expected the representative to leave the memory stick with the card as would be usual practice. Instead the representative posted the card with a memory stick and her business card but with no suggestion that she had already left one in the department. The complainant thus concluded that the representative had not left anything before which was why she did not mention it in her note and why she sent the card by post. The complainant also strongly objected to the inevitable conclusion that the mythical memory stick that was left had somehow been taken, presumably by a member of staff together with the note!

The complainant noted that equally it was not just the recollections of two people, particularly with reference to the conversation between his PA and the representative nor indeed was it true that 'there remained much which was based on personal recollection'. The receptionist heard the original conversation and it was reported back to the complainant within a few minutes (not recollected sometime later as was the case for the representative), the PA did not know the rules regarding needing to see a representative or not. Was it being suggested that this was not a true version of their account of the situation (and it was thus conversation with the PA that triggered the complaint in the first place)?

The complainant was surprised that the representative claimed not to have heard his PA's message until 4pm – would not a representative check the messages on their telephone after a meeting and before going home for the day? Was it more likely that this triggered the representative's attempts to telephone the centre and to ask if she could post the memory stick? Unfortunately, the representative did not call the centre three times as stated by Gilead – the number on the mobile telephone bill listed three times from 13.57 to 13.59 was the main hospital telephone and the centre did not have any telephone links with the hospital. The other number listed twice some minutes later (at 14.11 and 14.12) was not the centre's telephone number although it was similar. It still begged the question that if the representative was ringing to ask if she could post the memory stick – which was what happened – did she really come over to the centre; enter through a locked door that was apparently unlocked; leave a memory stick and note, neither of which had been found and subsequently post a reply card and memory stick with no mention of all of this?

The complainant alleged that having received the message on her telephone from his secretary, the representative decided to post the memory stick (and this was confirmed by her attempts to leave this message) and that no memory stick could have been left, or was left, in the centre without one of its staff knowing about it. Any other interpretation implied that two members of staff were not telling the truth and that someone in the department had taken the missing memory stick.

APPEAL BOARD RULING

The Appeal Board noted the further evidence submitted by each party. Differences in the parties' accounts remained. A judgement had to be made on the balance of probabilities.

The Appeal Board considered that it was most unfortunate that the representative had not had the memory stick with her at the initial call. The Appeal Board was also very concerned that at the appeal hearing the representative's line manager stated that he had not heard of what was said between the representative and the complainant's PA during the first visit to the centre, despite being in close proximity to the parties.

The Appeal Board noted from the representative that later in the day she had telephoned the hospital switch board and when she got through on the third attempt the hospital had given her the number for the centre. The representative had then twice tried to telephone the centre but no one had answered. It transpired that the number dialled was wrong by one digit. The representative stated that she had then returned to the centre. The representative could not recall how she had entered the centre however it was most likely that another person was using the door or the door was open. The representative stated that the reception was deserted so she left the memory stick that she had retrieved from her car together with a post-it note on the inside of the reception screen. The representative stated that she had not gone further into the centre as she considered that this would have made her an uninvited visitor. The Appeal Board noted that the complainant had stated that it was not possible to enter the reception when it was unmanned without ringing a bell and being let in. In any event the memory stick had not reached the complainant. The Appeal Board expressed concern that Gilead's written account of the telephone calls to the hospital and the centre differed from that of the representative at the appeal. However, the representative's account was consistent with the mobile telephone record provided by Gilead. The Appeal Board was also concerned that Gilead had not provided a comprehensive account in its initial response to the complaint. Each of Gilead's three submissions provided more detail.

The Appeal Board noted from the representative that she had accessed her voicemail at 1.55pm but had not received the voicemail left by the complainant's PA until 4pm, when she was on her way home. According to the representative this delay was apparently not unusual and was due to pockets of poor mobile telephone reception. On her return to home the representative had posted a further memory stick to the complainant together with the reply card, a note and her business card. The representative had not thought to include in her note that she had already left a memory stick at the centre.

The Appeal Board noted that both parties agreed that, at the very least, when the representative first visited the centre she had not got a memory stick with her but one had subsequently been sent by post and received by the complainant. It was not possible to determine precisely what had been said or taken place in the intervening time. There was a direct conflict of evidence. On the basis of the parties' submissions the Appeal Board did not consider that the complainant had satisfied the burden of proving that, on the balance of probabilities, the representative had failed to maintain a high standard of ethical conduct. The Appeal Board upheld the Panel's ruling of no breach of Clause 15.2. The appeal was not successful.

Complaint received **20 July 2009**

Case completed **15 October 2009**

CASE AUTH/2253/7/09

CONSULTANT PSYCHIATRIST v JANSSEN-CILAG

Promotion of Risperdal Consta

A consultant psychiatrist and visiting professor of psychiatry, complained about the promotion of Risperdal Consta (prolonged release risperidone) by Janssen-Cilag, Risperdal Consta was indicated for the maintenance treatment of schizophrenia in patients currently stabilised with oral antipsychotics.

The complainant stated that a Janssen-Cilag representative recently showed a presentation regarding the putative neuroprotective effects of risperidone. When the complainant protested that there was no clarity as to what was meant by 'neuroprotective effects', and that he would be concerned if there was no justificatory evidence for the claim that risperidone might have neuroprotective effects, he was sent a copy of Lieberman *et al* (2008). The paper did not justify any marketing campaign intended to imply neuroprotective effects for risperidone and in fact, appeared to be a review paper, regarding the potential effects of antipsychotics in general.

The complainant was therefore concerned, not necessarily at the actions of the representative, but at those who had designed a campaign to portray risperidone as having neuroprotective effects. The complainant was prepared to concede that risperidone might have neuroprotective effects, but there was currently not sufficient data to make this claim.

The detailed response from Janssen-Cilag is given below.

The Panel noted that Janssen-Cilag had provided part of the presentation; a sub-section which discussed relapse prevention and comprised 16 slides. The product logo appeared in the bottom right hand corner of each slide. The first 4 slides were headed 'Every relapse counts … give your patients the choice of Risperdal Consta earlier' and included the statement 'The first few years of illness have been proposed as a critical period during which an aggressive and relapsing course may lead to accruing morbidity and persistent deficits'. Six subsequent slides discussed early and late grey matter deficits in schizophrenia beneath the heading 'Recurrent relapses can lead to progressive brain tissue loss'. Below diagrams depicting early and late grey matter deficits was the claim 'Risperdal Consta can help prevent relapse and help patients achieve remission'. All the slides included the statement 'Latest thinking'. A pop-up box on slides 9 and 10 referred to a recent review (Lieberman *et al*) which suggested that some aytpicals had greater neuroprotective effects ie preventing or reversing the frontocortical grey matter decline seen in schizophrenia patients compared to conventional agents.

The Panel noted that the representatives were trained verbally on the presentation after which a guidance document was sent to them. This document instructed representatives to create a sense of urgency and to obtain agreement that relapse prevention was a key outcome. When showing the slides which discussed early and late grey matter deficits in schizophrenia (slide 5) representatives were instructed to discuss the impact of recurrent relapses and progressive brain tissue loss. Alongside the pop-up box which referred to neuroprotective effects (slide 9) representatives were told to discuss the 'suggested neuroprotective effects of aytpicals (Lieberman)'. No further guidance was given about the ensuing discussion on neuroprotective effects.

The Panel noted that Lieberman *et al*, a review article, concluded that schizophrenia 'possibly' involved a limited neurodegenerative component. Whilst more work was needed, the bulk of the data supported the authors' tentative conclusion that some antipsychotics, mainly the second generation antipsychotics, might be neuroprotective in schizophrenia.

The Panel considered that although there was no explicit claim about Risperdal Consta and neuroprotection, the slides very clearly linked the two. Representatives were instructed to refer to the suggested neuroprotective effects of atypical antipsychotics. In the Panel's view the overwhelming impression was that Risperdal Consta had neuroprotective effects. The material was misleading and incapable of substantiation in this regard. Consequently, the representative had failed to comply with all the relevant requirements of the Code. Breaches of the Code were ruled.

The Panel noted the clear link in the presentation between Risperdal Consta and neuroprotection and considered that in that regard it was inevitable that the briefing material advocated a course of action likely to lead to a breach of the Code and ruled accordingly.

A consultant psychiatrist and visiting professor of psychiatry, complained to the Medicines and Healthcare products Regulatory Agency (MHRA) about the promotion of Risperdal Consta (prolonged release risperidone) by Janssen-Cilag Ltd, copying his letter to the ABPI. The ABPI passed the letter to the Authority which treated it

as a complaint under the Code.

Risperdal Consta was indicated for the maintenance treatment of schizophrenia in patients currently stabilised with oral antipsychotics.

COMPLAINT

The complainant stated that a Janssen-Cilag representative recently showed him a PowerPoint presentation regarding the putative neuroprotective effects of risperidone. When the complainant protested that there was no clarity as to what was meant by 'neuroprotective effects', and that he would be concerned if there was no justificatory evidence for the claim that risperidone might have neuroprotective effects, he was sent a copy of Lieberman *et al* (2008). The paper did not justify any marketing campaign intended to imply neuroprotective effects for risperidone and in fact, appeared to be a review paper, regarding the potential effects of antipsychotics in general.

The complainant was therefore concerned, not necessarily at the actions of this representative, but at those who had designed a campaign to portray risperidone as having neuroprotective effects. He was prepared to concede that risperidone might have neuroprotective effects, but his underlying argument was that there was currently not sufficient data to make this claim.

When writing to Janssen-Cilag, the Authority asked it to respond in relation to Clauses 7.2, 7.4, 15.2 and 15.9 of the Code.

RESPONSE

Janssen-Cilag stated that it was committed to working in partnership with health professionals, and it acknowledged its responsibility to them. As a company, it took clinicians' concerns about its marketing activities very seriously.

The material in question was not intended to claim neuroprotective effects and Janssen-Cilag did not believe it did. Nor did Janssen-Cilag believe that the representative concerned made such a claim during the call. The material formed part of an electronic detail aid which was presented by representatives on laptop computers, and was made up of seven major sections: Introduction; Efficacy; Adherence; Value; How to Use; Choice; Tolerability. Janssen-Cilag believed that a sub-section in the Introduction which focused on the importance of relapse prevention was pertinent to this complaint. It aimed to raise awareness of the importance of relapse prevention in schizophrenia. It contained no claims about the neuroprotective effects of Risperdal Consta.

The page Janssen-Cilag believed was at issue provided information, supported by cited references, that recurrent relapses could lead to progressive brain tissue loss. It also showed images of grey matter deficits at baseline and 5 years later in patients with early onset schizophrenia. This link between relapse and brain tissue loss, which was supported by a credible body of evidence, was one of several reasons why preventing relapse was integral to the treatment of schizophrenia.

Janssen-Cilag submitted that its representatives had been trained on the appropriate use of the electronic detail aid verbally at a meeting in May 2009, after which they were sent a hard copy guidance document. The guidance stated that the relevant page was designed to highlight the impact of recurrent relapses, and of the potential for progressive brain tissue loss in schizophrenia. No guidance was given to make any link to Risperdal Consta or risperidone.

The final statement on the page in question 'Risperdal Consta can help prevent relapse and help patients achieve remission' referred to the clinical profile of Risperdal Consta. The statement was in a separate box at the foot of the page, and was supported by relevant literature about relapse prevention and remission data for Risperdal Consta.

A 'pop-up' link from this page, labelled 'Latest Thinking', stated 'A recent review of evidence suggests that some atypicals may have greater neuroprotective effects (i.e. preventing or reversing the frontocortical grey matter decline seen in schizophrenia patients) compared to conventional agents.' This statement accurately reflected the nature of the review article cited, which suggested that typical and atypical antipsychotics might have differential effects in terms of neuroprotection. This article was a recent, comprehensive review by leading experts on the latest thinking in the area of neurodegeneration in schizophrenia and it was this that was sent to the complainant following the representative's call.

Janssen-Cilag stated that the briefing document provided clear guidance to representatives that the information contained within this article provided a suggestion of neuroprotective effects of atypical antipsychotic medications. There was no guidance to them to make any link to Risperdal Consta or risperidone specifically, nor to draw any further conclusions from this paper.

To summarise, the briefing document confirmed that neuroprotection had not been presented as a claim for Risperdal Consta. The current thinking on the link between relapse and progressive brain tissue loss in schizophrenia had been included as relevant information to support the rationale for the importance of relapse prevention in the management of schizophrenia. The referenced information for the section in the 'pop-up' discussed atypical antipsychotics, of which risperidone was one of several available in the UK.

In all directive communication about Janssen-

Cilag's marketing strategy and guidance to the representatives there was no suggestion that they should link the concept of neuroprotection to Risperdal Consta specifically or that any such association was part of Janssen-Cilag's strategy. Wording and supportive guidelines were clear in relation to this.

Given the evidence cited above, Janssen-Cilag believed that the information in the section of the electronic detail in question was accurate, balanced and fair and did not breach Clause 7.2; the information was capable of substantiation and therefore not in breach of Clause 7.4. The representatives were adequately and appropriately briefed on the use of the materials so Janssen-Cilag believed that this was not in breach of Clause 15.9. The actions of the representative were consistent with the guidance given and, as the complainant was not concerned with the actions of the representative in question, Janssen-Cilag did not believe there had been a breach of Clause 15.2. Janssen-Cilag therefore did not agree there had been any breach of Clauses 7.2, 7.4, 15.2 or 15.9 in relation to the issues raised by the complainant.

However, as mentioned above, Janssen-Cilag took the views of health professionals very seriously. It strove to be a trusted partner to the health professionals with whom it interacted. It was extremely concerned that a clinician had found cause to complain about its marketing activities. In light of this, although it did not believe its materials to be misleading, as a clinician had raised concerns, it would further review them to ensure they transparently reflected Janssen-Cilag's intended communication.

PANEL RULING

The Panel noted that it had not been provided with a copy of the entire presentation at issue. Janssen-Cilag had identified and disclosed the section it considered pertinent to the complaint; a sub-section which discussed relapse prevention and comprised 16 slides. The product logo appeared in the bottom right hand corner of each slide. The first 4 slides were headed 'Every relapse counts … give your patients the choice of Risperdal Consta earlier' and included the statement 'The first few years of illness have been proposed as a critical period during which an aggressive and relapsing course may lead to accruing morbidity and persistent deficits'. Six subsequent slides discussed early and late grey matter deficits in schizophrenia beneath the heading 'Recurrent relapses can lead to progressive brain tissue loss'. Below diagrams depicting early and late grey matter deficits was the claim 'Risperdal Consta can help prevent relapse and help patients achieve remission'. All the slides included the statement 'Latest thinking'. A pop-up box on slides 9 and 10 referred to a recent review (Lieberman *et al*) which suggested that some aytpicals had greater neuroprotective effects ie preventing or reversing the frontocortical grey matter decline seen in schizophrenia patients compared to conventional agents.

The Panel noted that the representatives were trained verbally on the presentation at issue, after which the guidance document was sent to them. The guidance document instructed representatives to create a sense of urgency and to obtain agreement that relapse prevention was a key outcome. When showing the slides which discussed early and late grey matter deficits in schizophrenia (slide 5) representatives were instructed to discuss the impact of recurrent relapses and progressive brain tissue loss. Alongside the pop-up box which referred to neuroprotective effects (slide 9) representatives were told to discuss the 'suggested neuroprotective effects of aytpicals (Lieberman)'. No further guidance was given about the ensuing discussion on neuroprotective effects.

The Panel noted that Lieberman *et al*, a review article, concluded that schizophrenia 'possibly' involved a limited neurodegenerative component. Whilst more work was needed, the bulk of the data supported the authors' tentative conclusion that some antipsychotics, mainly the second generation antipsychotics, might be neuroprotective in schizophrenia.

The Panel considered that although there was no explicit claim about Risperdal Consta and neuroprotection, the slides very clearly linked the two. The first four slides referred to relapse and persistent deficits. The next six slides referred to relapses, progressive brain tissue loss and early and late grey matter deficits. All of these slides included a claim that Risperdal Consta '… can help prevent relapse and help patients achieve remission' and the product logo. Representatives were instructed to refer to the suggested neuroprotective effects of atypical antipsychotics. In the Panel's view the overwhelming impression was that Risperdal Consta had neuroprotective effects. The material was misleading and incapable of substantiation in this regard. A breach of Clauses 7.2 and 7.4 was ruled. Consequently, when presenting the material, the representative had failed to comply with all the relevant requirements of the Code. A breach of Clause 15.2 was ruled.

The Panel noted the clear link in the presentation between Risperdal Consta and neuroprotection and considered that in that regard it was inevitable that the briefing material advocated a course of action likely to lead to a breach of the Code. A breach of Clause 15.9 was ruled.

During its consideration of this matter the Panel noted the tentative conclusion of Lieberman *et al* ie that the atypical antipsychotics might have a neuroprotective effect in schizophrenia. The supplementary information to Clause 7.2, emerging clinical or scientific opinion, stated that when a clinical or scientific issue existed which had not been resolved in favour of one generally

accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material. In the Panel's view claims that a medicine or a class of medicines might do to something rarely negated the impression that they did do something. Lieberman *et al* was a literature review and the authors noted the inconsistency and variability of the results of the studies reviewed; not all of the atypical antipsychotics had been fully evaluated. The Panel asked that Janssen-Cilag be advised of its concerns in this regard.

Complaint received **29 July 2009**

Case completed **8 September 2009**

CASE AUTH/2255/8/09

GENERAL PRACTITIONER AND PHARMACIST v STIEFEL

Sponsored journal insert

A general practitioner and a pharmacist jointly complained about an insert on the management of mild and moderate acne vulgaris which had been published in GP journal. Stiefel marketed Duac Once Daily Gel (clindamycin 1% and benzoyl peroxide 5%) which was indicated for the treatment of mild to moderate acne vulgaris, particularly inflammatory lesions.

The complainants had previously alleged, *inter alia*, that the GP insert was disguised promotion for Duac (Case AUTH/2244/6/09). When the Authority had informed Stiefel of that complaint the company was not asked to consider the requirements of Clause 2; the complainants had not implicitly or explicitly alleged a breach of Clause 2. Due to a procedural error, the Panel nonetheless ruled a breach of Clause 2 which was consistent with other recent cases regarding sponsored inserts. The parties were informed of the initial ruling of a breach of Clause 2 and then the following day when the error was discovered by the Authority, immediately informed of the error and told that the ruling was null and void.

The complainants stated that whilst they did not specifically required Clause 2 to be considered in Case AUTH/2244/6/09, it did not negate its relevance. Indeed, as noted by the Authority there were recent precedents for this regarding company sponsored inserts purporting to be independent. Disguised promotion warranted a Clause 2 ruling. The complainants requested that the GP journal insert be subject to a complaint with regard to a breach of Clause 2 of the Code.

The detailed response from Stiefel is given below.

The Panel noted that the procedural error made in Case AUTH/2244/6/09 was unacceptable and should not have occurred. The procedural error had been discovered by the Authority, the ruling amended and the parties informed.

The Panel noted Stiefel's submission that Case AUTH/2255/8/09 had been pre-judged to be in breach; this was not so. Stiefel had not previously had the opportunity to make a detailed submission on the alleged breach of Clause 2. Any comments by Stiefel could now be considered by the Panel.

The Panel noted Stiefel's submission and its amended ruling in Case AUTH/2244/6/09. The Panel considered that the presentation of the insert was such as to reduce confidence in, and bring discredit upon the pharmaceutical industry. A breach of Clause 2 was ruled.

A general practitioner and a pharmacist jointly complained about an insert on the management of mild and moderate acne vulgaris which had been published in GP journal and provided as a service to medicine by Stiefel Laboratories. Stiefel's product Duac Once Daily Gel (clindamycin 1% and benzoyl peroxide 5%) was indicated for the treatment of mild to moderate acne vulgaris, particularly inflammatory lesions.

The complainants had previously alleged, *inter alia*, that the GP insert was disguised promotion for Duac (Point 9 in Case AUTH/2244/6/09). When the Authority had informed Stiefel of that complaint it had asked the company to consider the requirements of a number of clauses but had not cited Clause 2; the complainants had not implicitly or explicitly alleged a breach of Clause 2. Due to a procedural error, the Panel nonetheless ruled a breach of Clause 2 which was consistent with other recent cases regarding sponsored inserts. The parties were informed of the initial ruling of a breach of Clause 2 and then the following day when the error was discovered by the Authority they were immediately informed of the procedural error and told that ruling was null and void.

COMPLAINT

The complainants stated that whilst they might not have specifically required Clause 2 to be considered in Case AUTH/2244/6/09, it did not negate its relevance and the Panel was at liberty to require Stiefel to also consider the breach of this clause of the Code in respect of the GP insert. Indeed, as the Authority had noted in its explanatory letter, there were recent precedents for this regarding company sponsored inserts purporting to be independent. Disguised promotion warranted a Clause 2 ruling. The complainants requested that the GP journal insert be subject to a complaint with regard to a breach of Clause 2 of the Code.

RESPONSE

Stiefel noted that it had accepted the Panel's ruling in Case AUTH/2244/6/09 in which the GP journal insert was ruled in breach of Clauses 9.10 and 12.1 but not Clause 2.

Stiefel submitted that it concurred with the Panel's ruling because although the company was motivated to sponsor the Acne Working Group to meet a genuine need for a set of UK guidelines for the management of acne in general practice (and the opinions expressed in it were those of the experts not the company's) the printing of the company logo with the statement 'Provided as a service to medicine

by Stiefel' did not describe the full extent of the company's involvement. All materials mentioned in the complaint and all other materials related to the subject of the complaint were immediately withdrawn. Stiefel submitted that it had reviewed its processes and implemented further training to ensure its materials complied with the Code.

Stiefel believed that this case, Case AUTH/2255/8/09, and Case AUTH/2244/6/09, were one and the same as the initial ruling included a breach of Clause 2. This breach was subsequently withdrawn by the Authority as it was not part of the original complaint. The complainants were so informed and this prompted them to formally allege a breach of Clause 2.

Stiefel believed that Case AUTH/2255/8/09 had been already been pre-judged to be in breach of Clause 2. Therefore as the company had no additional points to make in submission to this fresh complaint, and in order to dispose of this case expeditiously, it considered that it had no option but to accept a breach of Clause 2.

PANEL RULING

The Panel noted that the procedural error made in Case AUTH/2244/6/09 was unacceptable and should not have occurred.

The Panel noted that in complaints from outwith the industry, or in cases arising from published criticism of the industry, the Director could ask the respondent company to consider the requirements of those clauses of the Code which were considered relevant to the matters raised (Paragraphs 5.1 and 6 of the Constitution and Procedure). The Panel could subsequently only make rulings under those clauses identified to the respondent company.

The Panel noted that the complainants had not alleged a breach of Clause 2 in Case AUTH/2244/6/09 and although a ruling of a breach of that clause might be consistent with other recent cases regarding sponsored inserts, Clause 2 was not raised in the initial correspondence with Stiefel and so the Panel could not make a ruling under that clause. In the absence of a specific allegation, the only action available to the Panel was to draw Stiefel's attention to its concerns in that regard. The procedural error had been discovered by the Authority. Action was taken to correct the procedural error and the parties were informed. The Panel had amended its ruling such that its raised concerns about Clause 2. The relevant paragraph was as follows: 'During the consideration of this matter the Panel was concerned to note that sponsored journal supplements which had similarly been ruled in breach of the Code because they were considered to be disguised promotion had also been ruled in breach of Clause 2. The Panel could not consider such a ruling in this case because the complainants had not explicitly or implicitly alleged that the supplement reduced confidence in or brought discredit upon the industry and so Stiefel had not been asked to consider the requirements of Clause 2. Nonetheless, the Panel requested that Stiefel be advised of its concerns in this regard.'

Case AUTH/2255/8/09

The Panel noted Stiefel's submission that Case AUTH/2255/8/09 had been pre-judged to be in breach; this was not so. Stiefel had not previously had the opportunity to make a detailed submission on the alleged breach of Clause 2. Any comments by Stiefel could now be considered by the Panel.

The Panel noted Stiefel's submission and its amended ruling in Case AUTH/2244/6/09. The Panel considered that the presentation of the insert was such as to reduce confidence in, and bring discredit upon the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **4 August 2009**

Case completed **18 September 2009**

CASE AUTH/2256/8/09

HEALTH AND SOCIAL CARE BOARD PRESCRIBING ADVISER v NAPP

Promotion of Targinact

A health and social care board prescribing adviser complained about a Targinact (prolonged release oxycodone and naloxone) presentation on a website (www.targetingpain.co.uk) sponsored by Napp. Targinact was indicated for the treatment of severe pain which could be adequately managed only with opioid analgesics. The usual starting dose for an opioid naïve patient was 10mg/5mg of oxycodone/naloxone at intervals of 12 hours.

Slide 7 of the presentation was headed 'How to prescribe Targinact tablets' and featured a highlighted box. The left hand side of the box stated 'Targinact tablets starting dose 10mg/5mg prolonged release 12-hourly oral tablets (total daily dose 20mg/10mg)'. The right hand side of the box was divided into two horizontally. The upper portion contained the statement 'Instead of … codeine, 8 x 30mg/500mg co-codamol tablets/day', and the lower portion contained the statement 'Instead of … tramadol 200mg/day'. Below the box the claim 'Prescribe Targinact 10mg/5mg tablets 12-hourly for patients with severe diagnosed back pain and severe osteoarthritis pain' was followed by 'The start dose of Targinact tablets is 10mg/5mg 12 hourly. This can be increased to 20mg/10mg 12 hourly if required' and 'Please refer to Targinact Summary of Product Characteristics (SPC) for further details'.

The complainant stated that the slide suggested that Targinact 10mg/5mg every 12 hours could be used instead of 8 x co-codamol 30mg codeine/500mg paracetamol tablets. The complainant alleged that this statement implied that these tablets had similar efficacy which was false and very misleading. Eight co-codamol 30/500 tablets were equivalent to 20mg morphine per day whereas Targinact 10mg/5mg twice daily was equivalent to 36mg morphine daily. This could prejudice patient safety.

The complainant stated that 8 co-codamol 30/500 was not equivalent to tramadol 200mg daily or Targinact 10mg/5mg twice daily in terms of morphine equivalence. Slide 7 did not state that Targinact was a controlled drug (Schedule 2). This information was also reproduced in printed material distributed to GPs and junior hospital doctors.

The detailed submission from Napp is given below.

The Panel noted that the Targinact SPCs stated that the usual starting dose for an opioid naïve patient was 10mg/5mg oxycodone/naloxone at 12 hourly intervals; this dose that was presented on the slide. The SPCs stated that patients already receiving opioids might be started on higher doses of Targinact depending on their previous opioid experience. The maximum daily dose of Targinact was 80mg/40mg oxycodone/naloxone.

With regard to co-codamol 30/500 the maximum daily dose of codeine was 240mg ie 8 tablets in any 24 hour period.

The Panel noted that the frequently asked question (FAQ) section of the website gave more detail than the slide. The response to the question 'How do I convert patients from other opioids?' included a table (which gave similar information about codeine and tramadol as slide 7 of the presentation) which was stated to be only a guide to the dose of Targinact that the patient might require and that inter-patient variability meant that titration to an appropriate dose might be required to provide optimal pain control. A footnote to the table gave a list of assumptions that had been used in compiling the data. Turning to the slide at issue the Panel noted that the data was presented without qualification. The phrase, 'instead of' implied that patients who had been on co-codamol 8 x 30mg/500mg or tramadol 200mg daily could be simply switched to Targinact 10mg/15mg twice a day which was not so. By Napp's own submission the conversion from one opioid to another was more complicated. Contrary to Napp's submission that all promotional material that provided conversion guidance included qualifying statements, there was no mention on the slide that the information had been provided as a guide only or of the need to individually titrate patients to an effective and well-tolerated dose. The slide did refer to increasing the dose to 20mg/10mg 12 hourly if required. In the Panel's view, although health professionals would know the difficulties of calculating equivalent doses of opioids and transferring patients from one to another it nonetheless considered that insufficient information had been given in the slide such that the comparison was misleading. The slide had to be capable of standing alone as regards the requirements of the Code. Breaches of the Code were ruled.

With regard to the alleged risk to patient safety, the Panel noted its ruling that slide 7 was misleading. Misleading material could potentially have a negative impact on patient safety. However, the Panel noted that Napp appeared to have used conservative dosage conversion ratios. It also

noted its comments above about health professionals' awareness of opioid equivalence issues and transferring patients. Targinact could be used in opioid naïve patients. The Panel did not consider that the slide warranted a further ruling of a breach on this point.

The Panel noted that Targinact was a controlled drug whereas co-codamol and Tramadol were not. The presentation did not mention that Targinact was a controlled drug. The legal classification was stated within the prescribing information which could be accessed from each page of the presentation. The Panel did not consider that the heading to the prescribing information 'Targinact tablets contain an opioid analgesic' was sufficient to ensure that readers were aware that Targinact was a controlled drug as submitted by Napp. There were opioid analgesics that were not controlled drugs. Although the Panel considered that it might have been helpful for it to be clearly stated on a page headed 'How to Prescribe Targinact' that Targinact was a controlled drug, on balance, the failure to do so was not misleading per se. No breach was ruled.

The Panel noted that the complainant referred to printed material but had not provided copies. The Panel examined the printed material supplied by Napp.

One page of a leavepiece for use with GPs and hospital specialists gave the same information as the slide at issue and included the additional statement 'This is a guide only, and patients should be individually titrated to an effective and well-tolerated dose'. The Panel noted that this qualification appeared as a footnote in small print at the bottom of the page and thus considered that it did not negate the impression that the codeine and tramadol doses could simply be changed for Targinact 10mg/5mg twice daily. The Panel considered that the leavepiece was therefore misleading and breaches of the Code were ruled. The Panel considered its comments above regarding patient safety applied to the leavepiece and no breach was ruled. Similarly the Panel considered its comments above regarding the failure to mention on the page headed 'How to prescribe Targinact' that Targinact was a controlled drug applied to the leavepiece and no breach was ruled.

Page 4 of a frequently asked questions document included a section headed 'How do I convert patients from other oral opioids?' The answer given included more information than given on slide 7 or in the leavepiece. The answer stated at the outset that the table of data was only a guide to the dose of Targinact that a patient might require and that inter-patient variability might mean that dose titration was required to provide optimal pain control. Below the table the assumptions and conversion factors applied to the table were listed. The Panel considered that this document was not misleading regarding the conversion and no breach was ruled.

A flyer used by the representatives alerted readers to the website and what was available on it. Although it was stated that the website included an introduction to Targinact there was no information given about comparable doses of co-codamol or tramadol. The Panel ruled no breach.

Overall, the Panel was concerned about the information on the website and the leavepiece. The Panel considered that high standards had not been maintained and a breach was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved for use as a sign of particular censure.

A health board prescribing adviser complained about the promotion of Targinact (prolonged release oxycodone and naloxone) by Napp Pharmaceuticals Limited. Targinact was indicated for the treatment of severe pain which could be adequately managed only with opioid analgesics. The usual starting dose for an opioid naïve patient was 10mg/5mg of oxycodone/naloxone at intervals of 12 hours.

The complainant stated that the material at issue was a presentation on www.targetingpain.co.uk/introducing-targin. Slide 7 of the presentation was headed 'How to prescribe Targinact tablets' and featured a highlighted box. In the left hand side of the box it was stated 'Targinact tablets starting dose 10mg/5mg prolonged release 12-hourly oral tablets (total daily dose 20mg/10mg)'. The right hand side of the box was divided into two horizontally. The upper portion contained the statement 'Instead of … codeine, 8 x 30mg/500mg co-codamol tablets/day', and the lower portion contained the statement 'Instead of … tramadol 200mg/day'. Below the box the claim 'Prescribe Targinact 10mg/5mg tablets 12-hourly for patients with severe diagnosed back pain and severe osteoarthritis pain' was followed by 'The start dose of Targinact tablets is 10mg/5mg 12 hourly. This can be increased to 20mg/10mg 12 hourly if required' and 'Please refer to Targinact Summary of Product Characteristics (SPC) for further details'.

COMPLAINT

The complainant stated that the promotional materials suggested that Targinact 10mg/5mg every 12 hours could be used instead of 8 x co-codamol 30mg codeine/500mg paracetamol tablets. The complainant alleged that this statement implied that these tablets had similar efficacy which was false and very misleading. Eight co-codamol 30/500 tablets were equivalent to 20mg morphine per day whereas Targinact 10mg/5mg twice daily was equivalent to 36mg morphine daily. This could pose a risk to a patient's safety.

The complainant stated that 8 co-codamol 30/500 was not equivalent to tramadol 200mg daily or Targinact 10mg/5mg twice daily in terms of morphine equivalence. It was not stated on slide 7 that Targinact was a controlled drug (Schedule 2).

This information was also reproduced in printed material distributed to GPs and junior hospital doctors.

When writing to Napp the Authority asked it to respond in relation to Clauses 2, 7.2, 7.3 and 9.1 of the Code.

RESPONSE

Napp strongly disagreed with the allegations, and did not believe that the Code has been breached, particularly in relation to Clauses 7.2, 7.3, 9.1 and 2.

With regard to the complainant's concern that the material referred to 'instead of … co-codamol 8 x 30/500mg tablets/day' or 'instead of … tramadol 200mg/day' and that promotion of Targinact in this way could 'pose a risk to patient safety', Napp referred to the Targinact SPCs which stated that the usual starting dose for an opioid naïve patient was 10mg/5mg of oxycodone/naloxone at 12-hourly intervals. Thus this dose could be used in patients with no prior experience of opioids, including codeine or tramadol. It was, therefore, not unreasonable or inconsistent with the SPCs to convert a patient who had an opioid requirement of 240mg codeine or 200mg tramadol to the recommended starting dose of 10mg/5mg Targinact tablets twice daily. The advice in the SPCs was considered appropriate and approved by the Medicines and Healthcare products Regulatory Agency (MHRA) during its appraisal of Targinact. Napp did not therefore consider that promotion in this way, which was consistent with the SPCs, posed a risk to patient safety.

The complainant stated that 8 x co-codamol 30/500mg was not equivalent to either tramadol 200mg daily or Targinact twice daily in terms of morphine equivalence. The fundamental issue related to analgesic equivalence (equianalgesia) between opioids which was based on conversion ratios. Equianalgesia referred to different doses of two agents that provided approximately equivalent pain relief. An equianalgesic dose referred to a dose that yielded roughly equivalent analgesia to a standard set in a given equianalgesic dose table. Most commonly, equianalgesic dose tables were standardised such that various opioid doses were provided relative to morphine.

Although equianalgesic dose tables were widely used to determine the new doses when converting from one opioid to another, there was a huge variation in published conversion ratios between different opioids. This was because converting opioid doses was currently based on pharmacokinetic data (such as bioavailability after oral administration) from observational and uncontrolled studies, often only using single doses, and on expert opinion and experience. Such studies often failed to account for inter-individual variations that played a prominent role in determining the appropriate ratio for each individual. Therefore the applicability of such published ratios for patients on long-term opioid therapy was the subject of much controversy and differences of opinion.

Napp had a strong heritage in the provision of opioid analgesics. Although the calculation of equianalgesic doses of opioids was a contested subject (as described above), health professionals required practical conversion guidance in order to make informed prescribing decisions. Therefore Napp believed it had a responsibility to provide guidance, where possible, in order to ensure that its opioid medicines were prescribed appropriately, whilst also highlighting that patients should be individually titrated to analgesic effect.

The material at issue suggested that Targinact 10mg/5mg twice daily could be used instead of co-codamol 8 x 30/500mg tablets per day (ie a total daily dose of 240mg codeine). This was derived from a two step process, based initially upon a conversion ratio of codeine to morphine of 6:1. So, 240mg codeine per day provided an equivalent total daily dose of 40mg morphine. The next step involved converting from morphine to oxycodone, and here a 2:1 conversion ratio had been used. Therefore it followed that a daily dose of 40mg morphine was equivalent to a daily dose of 20mg oxycodone or Targinact 10mg/5mg twice daily.

The suggestion that Targinact 10mg/5mg twice daily could be used instead of tramadol 200mg daily was based on the same process; initially a 5:1 conversion from tramadol to morphine which gave a morphine equivalence of 40mg, and subsequently the 2:1 conversion for morphine to oxycodone as described above.

Rationale for 6:1 dosage conversion ratio of codeine to morphine

Guidance for equianalgesic doses of codeine and morphine showed wide variability in the literature. As described above, this reflected the multiple inter-individual factors that were present, for example inter-patient variability in the efficacy and safety response to opioids due to tolerance and cross tolerance, pharmacokinetic and pharmacodynamic variability, use of co-analgesics and other CNS-active medicines, and psychological variables. Genetic factors also played a role, as it was known that due to polymorphisms in the hepatic microsomal CYP2D6 enzymes, approximately 7-10% of the population were poor-metabolisers of codeine and therefore obtained little or no analgesic effect from it, with 10-15% being intermediate metabolisers thus reducing the relative potency of codeine in such individuals when compared to morphine. Conversely it was also known that some individuals might be extensive (normal) or ultra-rapid metabolisers, which served to highlight the complexity that such genetic factors could add. In addition, estimates of dose equivalence were often based on single-dose studies and not repetitive dosing.

The literature suggested a wide range of

conversions for codeine to morphine when taken orally – between 3.3:1 and 10:1, with the majority of recommended conversion ratios based on clinical experience rather than firm scientific evidence. Recognising that the variation in the conversion ratios was wide, Napp used an approximate mid-point of the codeine to morphine range (ie 6:1) in order to provide some practical guidance for the physician as to where Targinact fitted in therapy relative to other products (in this case codeine) that were also used for severe non-malignant pain.

A number of references supported an approximately 6:1 dose conversion ratio of codeine:morphine. Rossi (2009) stated that 'a dose of approximately 200mg (oral) of codeine must be administrated to give analgesia approximately equivalent to 30mg (oral) of morphine' which equated to 6.7:1 codeine:morphine. This conversion ratio was also recommended by Manfredi (2005), Currie *et al* (2007) and Cherney and Foley (1996). Taking into account the dosage forms currently available for oral codeine in the UK, as well as for Targinact tablets, a 6:1 conversion provided practical guidance to the prescriber, realisable with the dosage strengths available. Indeed the Palliative Care Formulary, 3rd Edition (PCF3) recommended that, with any opioid switch, 'round the calculated dose up or down to the nearest convenient dose of the preparation concerned'.

The complainant suggested that co-codamol 8 x 30/500mg (ie 240mg codeine total) was equivalent to 20mg morphine per day. This was based on a codeine:morphine conversion ratio of 12:1. A conversion factor of 12:1 was based on the potency ratio of parenteral morphine to parenteral codeine and an assumption based on the absolute oral bioavailabilities of morphine and codeine, rather than on studies comparing the analgesic efficacy of these medicines administered orally.

Napp submitted that there were limited direct comparisons between oral oxycodone and oral codeine. Beaver *et al* (1978) looked at the oral:parenteral analgesic relative potency ratio for codeine and oxycodone independently and stated that 'whilst we are unaware of any controlled studies comparing oral oxycodone with oral codeine ... by calculating relative potencies across studies, it is possible to estimate that 10mg of oral oxycodone should be comparable in analgesic effect to 100mg of oral codeine'. This equated to a mean conversion ratio of codeine to oxycodone of 10:1 which was comparable to, and less conservative than, the 12:1 conversion ratio currently used by Napp. The 10:1 ratio of codeine:oxycodone was also employed in a study in children comparing the two in the treatment of pain due to suspected forearm fracture (Charney *et al* 2008).

Taking the above into account, Napp submitted that a dose conversion ratio of 6:1 for codeine to morphine was reasonable. Furthermore, the company was currently conducting a randomised, double-blind, clinical trial comparing the efficacy of Targinact tablets with co-codamol in the treatment of pain due to osteoarthritis and low back pain. This trial was a non-inferiority design, and compared the two treatments at doses Napp believed to be equivalent, based on a 6:1 codeine to morphine conversion, followed by a 2:1 morphine to oxycodone conversion as described above. This study had been evaluated by an independent ethics committee, and the principal investigator was an experienced pain consultant. These factors provided confidence that the relative doses of Targinact and co-codamol being used were appropriate.

Rationale for 5:1 dosage conversion ratio of tramadol to morphine

The material used a ratio of tramadol to morphine of 5:1 as Napp considered this represented standard clinical practice in the UK, as evidenced by local guidelines and the published literature.

The Targinact material referenced the conversion ratio of 5:1 for tramadol to morphine to the PCF3. However, in responding to this complaint, Napp had noted that this edition has been reprinted and now gave a conversion ratio of tramadol to morphine of 10:1. This meant that there were two versions of the PCF3 in circulation, containing different conversion ratios of tramadol to morphine. This difference between the conversion ratios had potential clinical implications, and yet the authors did not consider this significant enough to change the edition number or, at the very least, provide extensive communication of this change. Furthermore, the authors' rationale for significantly changing the conversion ratio for tramadol to morphine was based on 'extensive German clinical experience over many years', to which no specific evidence-based reference was given, thus highlighting the wide variability of such conversion ratios. A literature search identified ratios varying from 4:1 to 10:1, which showed the wide variability in the range of reported conversion ratios as for codeine.

Furthermore within individual patients, just as described for codeine, the opioid analgesic properties of tramadol were also affected by the hepatic CYP2D6 microsomal enzyme. The parent molecule was metabolised by CYP2D6 in the liver to the more potent opioid analgesic O-desmethyl tramadol. Therefore, depending on the genetic expression of CYP2D6 of the patient, they might be normal (extensive metabolisers), poor, intermediate or ultra-rapid metabolisers. This further complicated the derivation of a definitive opioid conversion ratio for tramadol.

Napp had conducted two in-house clinical studies directly comparing oral sustained release tramadol with oral prolonged release oxycodone in osteoarthritis patients with low back pain. These both demonstrated an analgesic equivalence of tramadol to oxycodone of 10:1, which was consistent with the guidance provided by the company for the relative doses of tramadol to the

oxycodone component of Targinact (ie 200mg tramadol/day was approximately equianalgesic to Targinact 10mg/5mg twice daily).

The complainant stated that '8 x co-codamol 30/500mg was not equivalent to tramadol 200mg daily' and therefore Napp had assumed that this aspect of the complaint might be directed towards the apparent equivalence between codeine and tramadol, rather than tramadol and morphine, or indeed tramadol and Targinact. As with oxycodone and codeine, there were few clinical studies comparing tramadol and codeine. While tramadol was considered more potent than codeine, Mullican and Lacy (2001) found an approximate 1:1 conversion ratio when tramadol/paracetamol was compared with codeine/paracetamol although Davis *et al* (2005) found that 200-250mg of tramadol produced the same degree of pain relief as 140mg of codeine plus 1400mg paracetamol, equivalent to a conversion ratio of approximately 1:1.5-1.8. Due to the lack of clarity regarding the relative potencies of tramadol and codeine, it was reasonable to use their respective potencies relative to morphine in order to give some guidance. On balance, Napp believed that based on the potencies of tramadol and codeine relative to morphine, as well as on the limited comparative data between the two, it was reasonable to suggest that 200mg of tramadol was approximately equivalent to 240mg of codeine.

Rationale for 2:1 dosage conversion ratio of morphine to oxycodone

There were wide inter-individual variations in the bioavailability of oral morphine and oxycodone; morphine ranged from 15 - 69%, whereas for oxycodone the mean bioavailability ranged from 37 - 87%. Thus depending on an individual's ability to absorb, distribute and metabolise morphine, the relative potency of oxycodone could in theory show a wide range. Indeed clinical studies had shown oral morphine to oxycodone conversions ratios ranged from 1:1 to 2.3:1, and therefore a 2:1 ratio reflected a conservative approach (Anderson *et al* 2001) when converting from morphine to oxycodone. Furthermore, the OxyContin (prolonged release oxycodone tablets) SPC stated that 'patients receiving oral morphine before OxyContin therapy should have their daily dose based on the following ratio: 10mg of oral oxycodone is equivalent to 20mg of oral morphine' and so a conversion ratio of 2:1 morphine:oxycodone was recommended by Napp as a guide. Using this conversion factor to convert from morphine to oxycodone, Targinact 10mg/5mg twice daily equated to 40mg and not 36mg morphine as stated by the complainant.

In summary, Napp firmly believed that the information presented for Targinact appropriately and responsibly reflected the balance of evidence regarding the comparative potency of codeine, tramadol and Targinact. The suggestion that Targinact 10mg/5mg twice daily could be used instead of total daily doses of 240mg codeine or 200mg tramadol was reasonable, supported by evidence and not misleading. Napp did not consider that it had breached Clauses 7.2 or 7.3 in this regard.

With regard to the failure to state that Targinact was a Schedule 2 controlled drug, Napp submitted that the Code required only that information relating to the legal classification of a drug be presented within the prescribing information (Clause 4.2). The legal classification of Targinact (CD (Sch2) Pom) was clearly stated in the prescribing information, to which there was a direct hyperlink on every page of the presentation on the website. Furthermore, Napp took very seriously the nature of the products that it promoted (ie controlled drugs), and for this reason the statement 'Targinact tablets contain an opioid analgesic' appeared at the top of the prescribing information to immediately alert the reader to this fact.

Slide 7 had a prominent display of the Targinact logo and non-proprietary name (ie oxycodone/naloxone) on the relevant webpage. The fact that Targinact contained the well known strong opioid oxycodone was therefore immediately obvious. In addition, the 'Overview' page of the module stated the therapeutic indication of Targinact, ie 'Severe pain, which can be adequately managed only with opioid analgesics. The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut' and thus provided clear information that this product was an opioid analgesic.

Napp stated that it was unclear exactly what the complainant meant by printed material. It assumed that the complainant meant the Targinact tablets 'Your Questions Answered' booklet (UK/TA-08046), which reproduced the 'Frequently Asked Questions' section of the website, and contained the dosage conversion information. This booklet explicitly provided information to the effect that the relative doses of Targinact, co-codamol and tramadol were provided as a guide only and that due to inter-individual variability, patients should be titrated to analgesic effect.

The complainant alleged that the promotion of Targinact 10mg/5mg twice daily as being equivalent to co-codamol 8 x 30/500mg or 200mg tramadol per day posed a potential risk to patient safety. Napp appreciated, as detailed above, that the calculation of equianalgesic doses of opioids was complex and that opioid dosage conversions could only be considered as a guide. Inter-patient variability required that each patient was carefully titrated to the appropriate dose. A statement to this effect was currently included in all promotional materials that provided conversion guidance. Indeed, wording to this effect is present specifically within the 'Frequently Asked Questions' section of the 'Introducing Targinact' module of the website at issue as well as the Targinact promotional booklets referred to by the complainant (which Napp assumed to be the 'Your Questions Answered' booklet).

Napp noted that the Targinact SPCs stated that 'The usual starting dose for an opioid naïve patient is 10mg/5mg of oxycodone hydrochloride/naloxone hydrochloride at 12 hourly intervals'. This implied that this dose could be used in patients with no prior experience of opioids, including codeine or tramadol. Bearing this in mind, it was therefore not unreasonable, nor inconsistent with the SPCs, for a patient who had reached an opioid requirement of 240mg codeine or 200mg tramadol to be converted to Targinact 10mg/5mg tablets twice daily, and hence would not be considered to jeopardise patient safety when done appropriately, following the guidance as described above. Indeed the British National Formulary recommended that in opioid naïve patients, the starting dose of prolonged release morphine preparations was usually 10 - 20mg 12-hourly (considered therapeutically equivalent to Targinact 5mg/2.5mg-10mg/5mg 12-hourly), and to replace a weaker opioid analgesic the starting dose was usually 20-30mg 12-hourly (considered therapeutically equivalent to Targinact 10mg/5mg-20mg/10mg 12-hourly). This national guidance was consistent both with the Targinact SPCs and with the conversion guidance in the promotional materials.

In conclusion, published opinions varied widely regarding the most appropriate conversion ratios to use. However, Napp recognised that health professionals relied on clear and practical conversion guidance, realisable with the dosage forms available, in order to make informed clinical decisions when prescribing opioids. Therefore Napp believed it had a responsibility to provide this type of guidance, where possible, based on the balance of the available evidence in order to ensure that its opioid medicines were prescribed appropriately and responsibly.

In response to a request for further information, Napp explained that the presentation at issue was available to health professionals through the 'Targeting Pain' website. This website was initiated and funded by Napp and provided in association with Pulse as a service to pain management with Targinact promotional material only included within the section for health professionals. The website had been promoted to health professionals via digital, email and print promotion; details were provided. The website was also advertised on certain Targinact promotional items, for example, a leavepiece used with GPs and hospital specialists (ref UK/TA-09105). Sales representatives promoted the website using a flyer (ref UK/FT-09044). The website was not used proactively by sales people as a training tool.

PANEL RULING

The Panel noted that the Targinact SPCs stated that the usual starting dose for an opioid naïve patient was 10mg/5mg oxycodone/naloxone at 12 hourly intervals. It was this dose that was presented on the slide at issue. The SPCs stated that patients already receiving opioids might be started on higher doses of Targinact depending on their previous opioid experience. The maximum daily dose of Targinact was 80mg/40mg oxycodone/naloxone.

With regard to co-codamol 30/500 the maximum daily dose of codeine was 240mg ie 8 tablets in any 24 hour period.

The Panel noted Napp's comments that although equianalgesic dose tables were widely used to determine the new doses when converting from one opioid to another, it was well recognised that there was a huge variation in published conversion ratios between different opioids. There was also inter-patient variability including, *inter alia*, genetic factors which determined how quickly patients metabolised codeine or tramadol. The Panel noted Napp's submission that it believed it had a responsibility to provide guidance where possible in order to ensure that its opioid medicines were prescribed appropriately whilst also highlighting that patients should be individually titrated.

The Panel noted that the frequently asked question (FAQ) section of the website gave more detail than the slide. The response to the question 'How do I convert patients from other opioids?' included a table (which gave similar information about codeine and tramadol as slide 7 of the presentation) which was stated to be only a guide to the dose of Targinact that the patient might require and that inter-patient variability meant that titration to an appropriate dose might be required to provide optimal pain control. A footnote to the table gave a list of assumptions that had been used in compiling the data. Turning to the slide at issue the Panel noted that the data was presented without qualification. The phrase, 'instead of' implied that patients who had been on co-codamol 8 x 30mg/500mg or tramadol 200mg daily could be simply switched to Targinact 10mg/15mg twice a day which was not so. By Napp's own submission the conversion from one opioid to another was more complicated. Contrary to Napp's submission that all promotional material that provided conversion guidance included qualifying statements, there was no mention on the slide that the information had been provided as a guide only or of the need to individually titrate patients to an effective and well-tolerated dose. The slide did refer to increasing the dose to 20mg/10mg 12 hourly if required. In the Panel's view, although health professionals would know the difficulties of calculating equivalent doses of opioids and transferring patients from one to another it nonetheless considered that insufficient information had been given in the slide such that the comparison was misleading. The slide had to be capable of standing alone as regards the requirements of the Code. Breaches of Clauses 7.2 and 7.3 were ruled.

With regard to the alleged risk to patient safety, the Panel noted its ruling that slide 7 was misleading. Misleading material could potentially have a negative impact on patient safety. However, the

Panel noted that Napp appeared to have used conservative dosage conversion ratios. It also noted its comments above about health professionals' awareness of opioid equivalence issues and transferring patients. Targinact could be used in opioid naïve patients. The Panel did not consider that the slide warranted a further ruling of a breach of Clause 7.2 on this point and no breach was ruled.

The Panel noted that Targinact was a controlled drug whereas co-codamol and Tramadol were not. The presentation did not mention that Targinact was a controlled drug. The legal classification was stated within the prescribing information which could be accessed from each page of the presentation. The Panel did not consider that the heading to the prescribing information 'Targinact tablets contain an opioid analgesic' was sufficient to ensure that readers were aware that Targinact was a controlled drug as submitted by Napp. There were opioid analgesics that were not controlled drugs. Although the Panel considered that it might have been helpful for it to be clearly stated on a page headed 'How to Prescribe Targinact' that Targinact was a controlled drug, on balance, the failure to do so was not misleading per se. No breach of Clause 7.2 was ruled.

The Panel noted that the complainant referred to printed material but had not provided copies. The Panel examined the printed material supplied by Napp.

Firstly the leavepiece (ref UK/TA-09105). One of the pages gave the same information as the slide at issue and included the additional statement 'This is a guide only, and patients should be individually titrated to an effective and well-tolerated dose'. The Panel noted that this qualification appeared as a footnote in small print at the bottom of the page and thus considered that it did not negate the impression that the codeine and tramadol doses could simply be changed for Targinact 10mg/5mg twice daily. The Panel considered that the leavepiece was therefore misleading and breaches of Clauses 7.2 and 7.3 were ruled. The Panel considered its comments above regarding patient safety applied to the leavepiece and no breach of Clause 7.2 was ruled. Similarly the Panel considered its comments above regarding the failure to mention on the page headed 'How to prescribe Targinact' that Targinact was a controlled drug applied to the leavepiece and no breach of Clause 7.2 was ruled.

The frequently asked questions document (ref UK/TA-08046) included on page 4 a section headed 'How do I convert patients from other oral opioids?' The answer given included more information than given on slide 7 or in the leaflet. The answer stated at the outset that the table of data was only a guide to the dose of Targinact that a patient might require and that inter-patient variability might mean that dose titration was required to provide optimal pain control. Below the table the assumptions and conversion factors applied to the table were listed. The Panel considered that this document was not misleading regarding the conversion and no breach of Clauses 7.2 and 7.3 was ruled.

The flyer used by the representatives (ref UK/FT-09044) alerted readers to the website and what was available on it. Although it was stated that the website included an introduction to Targinact there was no information given about comparable doses of co-codamol or tramadol. The Panel ruled no breach of Clauses 7.2 and 7.3.

Overall, the Panel was concerned about the information on the website and the leavepiece. The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved for use as a sign of particular censure.

Complaint received **6 August 2009**

Case completed **5 October 2009**

CASE AUTH/2257/8/09

VOLUNTARY ADMISSION BY FERRING

Information sent to patient group

Ferring voluntarily admitted that its public relations (PR) agency had sent unapproved copy about Firmagon (degarelix) to a patient organisation. The matter had come to light during the investigation of concerns raised by a competitor company. Firmagon was indicated for the treatment of advanced prostate cancer.

The action to be taken by the Authority in relation to a voluntary admission by a company was set out in the Constitution and Procedure which stated, *inter alia*, that the Director should treat the matter as a complaint if it related to a potentially serious breach of the Code. The provision of inappropriate information to the public and/or a patient organisation was a potentially serious matter and the Director decided to treat the matter as a complaint.

Ferring submitted that it was appropriate to provide the patient organisation with information about Firmagon, a new treatment for hormone deprivation therapy of advanced prostate cancer. Ferring gave the PR agency an approved press release about the launch of Firmagon for it to give to outside agencies including the patient organisation. No other briefing materials should have been provided to external agencies, including the patient organisation, without the prior approval of Ferring. However, following discussions with the patient organisation, the PR agency, unbeknown to Ferring emailed an edited version of the approved press release from which the patient organisation developed content for its website.

Ferring did not consider that the information emailed to the patient organisation fully and properly reflected the content of the approved press release. In particular: it omitted background information about prostate cancer; a consultant urologist's clinical opinion about the place of Fimagon; information about side effects and references; it added text that exaggerated the time taken by LHRH agonists to achieve castrate levels of testosterone and the statement 'Ask your doctor for more information about FIRMAGON' and it amended the text '… aimed at patients has been produced by Ferring Pharmaceuticals who hold the marketing authorisation FIRMAGON …' to '… aimed at patients has been produced by Ferring Pharmaceuticals who make FIRMAGON…'.

These changes significantly altered the balance of the information from that presented in the approved press release. The PR agency told Ferring that the patient organisation had requested simplified information with a limited word count and so the two worked together to produce the text that was ultimately provided. Ferring did not consider that it was acceptable for the PR agency to amend and provide copy to the patient organisation without its prior approval.

Following the provision of the non-approved copy, the home page for the patient organisation contained a link entitled 'DEGARELIX (Firmagon). More details about this new drug here – and how to order your free DVD'. Details of the DVD 'Progress for a Healthy Lifestyle: A Guide for Men on Hormone Therapy for Prostate Cancer' were provided. The information contained on the page was essentially the same as the text provided by the PR agency. This was set up by the patient organisation following the provision of the information from the PR agency together with a few samples of the DVD, which the patient organisation had endorsed. Ferring acknowledged that the juxtaposition in a link box on the patient organisation homepage, for details concerning Firmagon and the offer of the DVD was not satisfactory. Ferring emailed the patient organisation to ask it to separate the DVD information from the degarelix information and provide a new link to information on the DVD and how to get it from the patient organisation.

Changes were made to the patient organisation website about a month after the website went live.

Ferring took this situation extremely seriously and had had urgent detailed discussions to establish the circumstances. A review of the PR agency established that there were no other similar occurrences and that this was a one-off event that occurred because it wished to assist a patient organisation with limited resources.

Ferring told all relevant staff about the matter and would review of all agency agreements to ensure that there was no repeat.

The detailed response from Ferring is given below.

The Panel noted that Ferring's PR agency had provided unapproved copy about Firmagon. The Panel noted Ferring's submission that its PR agency had worked independently with the patient organisation. The Panel noted that companies were responsible for information about their products issued by their PR agencies. If this were not so it would be possible for agencies to act beyond the scope of their agreement with the pharmaceutical company, in a way which the company could not do itself and so avoid the

restrictions of the Code. It was important that pharmaceutical companies actively managed their PR agencies in this regard and ensured that they had Code compliant systems in place.

It was not unacceptable to give information about prescription only medicines to patient organisations but its content and provision had to comply with the Code. Transparency was a key requirement.

It appeared from an email dated 22 June from the PR agency to the patient organisation that the agency had in effect provided camera ready copy. Ferring had submitted that the published material was essentially the same as the text provided by its agency. It was unclear whether the original request for copy by the patient organisation was unsolicited. This was thought to be unlikely given the distribution of the DVD was to be from the patient organisation website. The email however was dated 22 June whereas the press release was dated 24 June. Firmagon was launched on 22 June. Irrespective of the status of the original request the material provided still had to comply with the Code.

The Panel was very concerned about the amendments made to the approved press release; Important information had been omitted and text had been amended.

With concern, the Panel noted in addition to those changes to the press release cited by Ferring a sentence in the approved press release which read 'Firmagon doesn't cause these initial hormone surges and so doctors don't prescribe anti-androgen therapy to counteract this, avoiding associated side effects and offering an effective monotherapy' had been changed to read '… avoiding associated side-effects *and ensuring that men with prostate cancer only have to take one medication instead of two*' (emphasis added). The Panel noted Ferring's acknowledgement that the totality of the changes significantly altered the balance of the information presented in the press release.

The text provided to the patient organisation had not been certified as required by the Code and a breach was ruled. The changes made to the press release were such that the information was misleading and not presented in a balanced way; information about side effects had been omitted and the time taken by a class of competitor products to achieve castration levels of testosterone had been exaggerated. Also mention was made of only having to take one medicine instead of two. In the Panel's view the amended press release would encourage members of the public to ask their health professional to prescribe a specific prescription only medicine, Firmagon. The material failed to comply with the Code and a breach was ruled.

The Panel was concerned about the misleading nature of the changes made to the press release. The agency had in effect provided the patient organisation with copy ready for publication although the patient organisation was told it could 'tweak' the copy or simplify the language. The Panel noted that as published on the patient organisation website the material did not refer to Ferring's role in the creation of the material. It appeared to be patient organisation material. The Panel considered that the changes made to the material were such that Ferring via its agency had in effect sought to influence text presented as patient organisation material in a manner favourable to its own interest. A breach of the Code was ruled.

The Panel was very concerned about the misleading content of the material and the relationship with the patient organisation as evidenced by the email correspondence. The email dated 22 June from the agency to the patient organisation gave the overall impression that publication of the Firmagon copy and the offer of the DVD on the patient organisation website were an integral part of the Firmagon launch strategy. Reference was made to measuring the number of website hits to measure impact. Whilst this was not necessarily unacceptable it was important that readers were aware of Ferring's role in relation to the creation of material published on the patient organisation's website. The Panel noted that Ferring had not raised this point specifically in its voluntary admission.

The Panel was concerned that Ferring only discovered this matter when so informed by a competitor company. Whilst it was unfortunate that Ferring had been placed in this position by its agency which appeared to have ignored the agreement between the parties, Ferring was nonetheless responsible for activity undertaken on its behalf. The Panel noted that misleading material had been provided to a patient organisation for publication. Information about side effects had been omitted. The arrangement was not transparent. High standards had not been maintained. A breach of the Code was ruled. On balance the Panel considered that the circumstances brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Ferring Pharmaceuticals Ltd voluntarily admitted that its public relations (PR) agency had sent unapproved copy about Firmagon (degarelix) to a patient organisation. The matter had come to light during the investigation of concerns raised by a competitor company. Firmagon was indicated for the treatment of advanced prostate cancer.

The action to be taken by the Authority in relation to a voluntary admission by a company was set out in Paragraph 5.4 of the Constitution and Procedure which stated, *inter alia*, that the Director should treat the matter as a complaint if it related to a potentially serious breach of the Code. The

provision of inappropriate information to the public and/or a patient organisation was a potentially serious matter and the Director decided to treat the matter as a complaint.

COMPLAINT

Ferring submitted that it was appropriate to provide the patient organisation with information containing basic facts about Firmagon, a new treatment for hormone deprivation therapy of advanced prostate cancer. Ferring provided the PR agency with an approved press release, for communication to outside agencies including the patient organisation. This press release related to the launch of Firmagon on 22 June 2009. No other briefing materials should have been provided to external agencies, including the patient organisation, without the prior approval of Ferring. However, following discussions with the patient organisation, the PR agency emailed an edited version of the approved press release from which the patient organisation developed content for its website. Copies of the approved press release and the information provided to the patient organisation by the PR agency were provided. Ferring noted that the email containing the non-approved copy was blind circulated to a senior brand manager at Ferring at the same time as it was sent to the patient organisation. Unfortunately, the email arrived at a very busy period during the launch week and was viewed on a hand held device rather than a computer and so the attachment was not opened. There was no reason to believe from the contents of the email that the information provided was not the approved press release and so the attachment was not later reviewed.

Ferring noted that Paragraph 12 of the Guidelines on Company Procedures Relating to the Code of Practice, gave information about interaction between pharmaceutical companies and patient organisations: 'Pharmaceutical companies can interact with patient organisations or any user organisation such as disability organisations, carer or relative organisations and consumer organisations to support their work, including assistance in the provision of appropriate information to the public, patient and carers'.

From this guidance, Ferring was unclear whether it was acceptable under the Code for the PR agency to work with the patient organisation in the way that it did, in order to assist the patient organisation to produce the text it wished to place on its website.

Ferring only learnt about this after the event, when it found out that the content on the patient organisation website was not consistent with the information that would have been provided by the approved press release. Ferring did not consider the information provided to the patient organisation by the PR agency fully and properly reflected the content of the approved press release.

In particular, following discussion with the patient organisation, the PR agency made some significant changes to the approved press release:

- The omission of background information about prostate cancer.
- The omission of comments by a consultant urologist, which gave a clinical opinion about the place of Firmagon as a new option for androgen deprivation therapy in patients with advanced hormone-dependent prostate cancer.
- The addition of text that exaggerated the time taken by LHRH agonists to achieve castrate levels of testosterone by adding '(and longer)' in the following text '… unlike existing hormone treatments which take up four weeks (and longer) to reduce testosterone to the required levels'. This was amended by the PR agency with the intention of reflecting the situation in which the use of an anti-androgen preceded the administration of an LHRH agonist, which was not a claim that Ferring supported as sustainable.
- The omission of information regarding side effects.
- The addition of the text 'Ask your doctor for more information about FIRMAGON'.
- Amending the text '… aimed at patients has been produced by Ferring Pharmaceuticals who hold the marketing authorisation FIRMAGON …' to '… aimed at patients has been produced by Ferring Pharmaceuticals who make FIRMAGON …'.
- The omission of references.

Ferring acknowledged that these changes significantly altered the balance of the information from that presented in the approved press release. The PR agency told Ferring that the patient organisation had requested simplified information with a limited word count and so the two organisations worked together to produce the wording that was ultimately provided to the patient organisation by the PR agency. Ferring did not consider that it was acceptable for the PR agency to make amendments and provide any copy to the patient organisation without its prior approval.

Following the provision of the non-approved copy, the home page for the patient organisation contained a link entitled 'DEGARELIX (Firmagon). More details about this new drug here – and how to order your free DVD'. Details of the DVD 'Progress for a Healthy Lifestyle: A Guide for Men on Hormone Therapy for Prostate Cancer' were provided. The information contained on the page was essentially the same as the text provided by the PR agency. This was set up by the patient organisation following the provision of the information from the PR agency together with a small number of samples of the DVD, which the patient organisation had endorsed. Ferring understood that this went live on 24 June. Ferring acknowledged that the juxtaposition in a link box on the patient organisation homepage, for details concerning Firmagon and the offer of the DVD was

not satisfactory. Ferring emailed the patient organisation on 25 June to ask it to separate the DVD information from the degarelix information and provide a new link to information on the DVD and how to get it from the patient organisation. In subsequently telephone calls (26 and 29 June) Ferring was told that the website was managed by a trustee of the charity who would take account of the request but as this was an independent patient organisation, he would decide how and when the relevant changes would be made.

Ferring was then informed by the patient organisation that changes were being made on 3 July. Changes were made to the patient organisation website on 6 July that consisted of the addition of a separate link to details about the DVD, although the reference to the DVD was not removed from the link to degarelix or from the degarelix information page.

On 24 July, Ferring once again asked that the information on the patient organisation website be updated as quickly as possible, and the website was revised later that day, to take account of all Ferring's concerns. Information about the DVD was no longer linked to information about Firmagon and the information provided about Firmagon was acceptable to Ferring. Copies were provided of the relevant pages of the website as they appeared on 7 August.

Ferring took this situation extremely seriously and had had urgent detailed discussions with the PR agency to establish the circumstances surrounding this issue, and to ensure that appropriate procedures were put in place to prevent a repeat of this unacceptable practice. A review of the PR agency established that there were no other similar occurrences and that this was a one-off event that occurred because it wished to assist a patient organisation with limited resources.

Ferring had told all relevant staff about this matter and would review all agency agreements to ensure that their was no repeat.

When writing to Ferring, the Authority asked it to respond in relation to Clauses 2, 9.1, 14.3, 22.2 and 23.6 of the Code.

RESPONSE

Ferring believed that a key aspect of this case was that of how the text given to the patient organisation by the PR agency was decided upon and agreed between those two parties. Under Clause 23.1 pharmaceutical companies were allowed to work with patient organisations.

In an initial meeting to discuss the disease awareness DVD, the patient organisation agreed to endorse the DVD and wished to offer it through its website. No payment to the patient organisation was discussed, offered or paid. No agreement had been entered into between Ferring and the patient organisation, other than that Ferring would supply it with disease awareness DVDs free of charge and it in turn would offer them at no charge to patients who visited its website. Ferring had not provided, nor currently provided any additional financial or other support to the patient organisation.

Whilst Ferring accepted that the text that was provided by the PR agency following a telephone conversation with the patient organisation would not have complied with the Code if it were provided unsolicited, the text was prepared only after a telephone conversation between the PR agency and the chief executive of the patient organisation. The text was intended to help to meet the patient organisation's immediate needs because its staff were extremely busy with other activities at that time. The PR agency did not intend to provide inappropriate material and the changes made to the approved press release reflected the needs and usual style for content on the patient organisation's website eg the patient organisation normally included a recommendation that patients discussed their treatment needs and options with their own doctor.

In this instance, the PR agency worked independently with the patient organisation, with good intentions. However, Ferring acknowledged that this was not appropriate, and the actions of the PR agency resulted in the provision of text that had not been approved by Ferring. In mitigation, however, as soon as Ferring became aware of this action steps were taken to correct the situation, as outlined above.

In addition, the actions of the PR agency contravened its agreement with Ferring, which stated, *inter alia*:
'[The Agency] agrees, in addition, not to make any statement on Ferring's behalf or concerning Ferring to the press, media, investors, brokers, banks, financial analysts and/or any other person unconnected with Ferring without the prior approval of Ferring. This Clause 4 together with Clauses 6, 9 and 10 will survive any expiry or termination of this Agreement.'

Ferring did not believe that there had been a breach of Clause 2, which related to promotional activities or materials that brought discredit upon, or reduced confidence in, the pharmaceutical industry, either by positive action or inadequate action. Ferring believed that the PR agency worked in good faith to try to meet the needs of the patient organisation. The text provided to the patient organisation did not exaggerate the properties of Firmagon, although Ferring acknowledged that it lacked balance, for example, by excluding information relating to side effects. As stated above, the PR agency's actions contravened its agreement with Ferring, and it should be noted that when Ferring became aware of the situation, steps were taken that resulted in the removal of the original copy and subsequent posting of appropriate information on the patient

organisation website as quickly as possible. Ferring noted that a breach of Clause 2 denoted particular censure and it did not consider that the circumstances surrounding this event related in type or scale to the examples of activities which could lead to a breach of this clause.

Ferring did not consider that there had been a breach of Clause 9.1, which related to the maintenance of high standards in promotional activities. As previously noted, the PR agency had tried to assist the patient organisation by providing text for its website in accordance with the patient organisation's needs. In addition, the PR agency contravened the agreement between it and Ferring to seek prior approval for the copy that was provided to the patient organisation.

Ferring accepted that this matter might be in breach of Clause 14.3 since the PR agency essentially provided the patient organisation with uncertified copy, albeit following a telephone conversation with the patient organisation which resulted in the provision of text was intended to meet the needs of the patient organisation.

Ferring accepted that this matter might be in breach of Clause 22.2 since the information provided to the patient organisation lacked balance, for example, by excluding information relating to side effects, and included the statement 'Ask your doctor for more information about Firmagon' albeit following a telephone conversation with the patient organisation, which resulted in the provision of text intended to meet the needs of the patient organisation.

Ferring did not consider that there had been a breach of Clause 23.6, which related to a company attempting to influence patient organisation material in a manner favourable to its own commercial interests. As previously described, the PR agency had tried to assist the patient organisation to prepare text for its website that was in accordance with the patient organisation's needs. Ferring did not believe that the text provided was promotional, or that it would raise unfounded expectations in patients.

Ferring had reviewed all agreements with agencies to ensure that provisions were in place to require that agencies working on its behalf provided only approved communications to approved recipients.

PANEL RULING

The Panel noted that Ferring's PR agency had provided unapproved copy about Firmagon to a patient organisation. The Panel noted Ferring's submission that its PR agency had worked independently with the patient organisation. The Panel noted that companies were responsible for information about their products issued by their PR agencies (Clause 22.5). If this were not so it would be possible for beyond the scope of their agreement with the pharmaceutical company and in a way which the company could not do itself and so avoid the restrictions of the Code. It was important that pharmaceutical companies actively managed their PR agencies in this regard and ensured that they had Code compliant systems in place.

It was not unacceptable to make available information about prescription only medicines to patient organisations but its content and provision had to comply with the Code particularly Clauses 22 and 23 and the relevant supplementary information. Transparency was a key requirement.

It appeared from an email dated 22 June from the PR agency to the patient organisation that the agency had in effect provided camera ready copy. Ferring had submitted that the published material was essentially the same as the text provided by its agency. It was unclear whether the original request for copy by the patient organisation was unsolicited. This was thought to be unlikely given the distribution of the DVD was to be from the patient organisation website. The email however was dated 22 June whereas the press release was dated 24 June. Firmagon was launched on 22 June. Irrespective of the status of the original request the material provided still had to comply with the Code.

The Panel was very concerned about the amendments made to the approved press release. Certain important information had been omitted such as information about side effects. Text had been amended: the phrase 'and longer' had been added to a sentence about onset of action which now read 'This is unlike existing hormone treatment which can take up to four weeks **(and longer)** to reduce testosterone to the required levels' (emphasis added), an amendment which Ferring acknowledged exaggerated the time taken by LHRH agonists to achieve castration levels of testosterone.

With concern, the Panel noted in addition to those changes to the press release cited by Ferring a sentence in the approved press release which read 'Firmagon doesn't cause these initial hormone surges and so doctors don't prescribe anti-androgen therapy to counteract this, avoiding associated side effects and offering an effective monotherapy' had been changed to read '… avoiding associated side-effects **and ensuring that men with prostate cancer only have to take one medication instead of two**' (emphasis added). The Panel noted Ferring's acknowledgement that the totality of the changes significantly altered the balance of the information presented in the press release.

The text provided to the patient organisation had not been certified as required by Clause 14.3; a breach of that clause was ruled. The changes made to the press release were such that the information was misleading and not presented in a balanced way; information about side effects had been

omitted and the time taken by a class of competitor products to achieve castration levels of testosterone had been exaggerated. Also mention was made of only having to take one medicine instead of two. In the Panel's view the amended press release would encourage members of the public to ask their health professional to prescribe a specific prescription only medicine, Firmagon. The material failed to comply with Clause 22.2 and a breach of that clause was ruled.

The Panel was concerned about the misleading nature of the changes made to the press release. The agency had in effect provided the patient organisation with copy ready for publication although the patient organisation was told it could 'tweak' the copy or simplify the language. The Panel noted that as published on the patient organisation website the material did not refer to Ferring's role in the creation of the material. It appeared to be patient organisation material. The Panel considered that the changes made to the material were such that Ferring via its agency had in effect sought to influence text presented as patient organisation material in a manner favourable to its own interest. A breach of Clause 23.6 was ruled.

The Panel was very concerned about the misleading content of the material and the relationship with the patient organisation as evidenced by the email correspondence. The email dated 22 June from the agency to the patient organisation gave the overall impression that publication of the Firmagon copy and the offer of the DVD on the patient organisation website were an integral part of the Firmagon launch strategy. Reference was made to measuring the number of website hits to measure impact. Whilst this was not necessarily unacceptable it was important that readers were aware of Ferring's role in relation to the creation of material published on the patient organisation's website (Clauses 9.10 and 23.8 referred). The Panel noted that Ferring had not raised this point specifically in its voluntary admission.

The Panel was concerned that Ferring only discovered this matter when so informed by a competitor company. Whilst it was unfortunate that Ferring had been placed in this position by its agency which appeared to have ignored the agreement between the parties, Ferring was nonetheless obliged to take responsibility for activity undertaken on its behalf. The Panel noted that misleading material had been provided to a patient organisation for publication. Information about side effects had been omitted. The arrangement was not transparent. High standards had not been maintained. A breach of Clause 9.1 was ruled. On balance the Panel considered that the circumstances brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

During its consideration of this case the Panel noted that the home page of the patient organisation website featured a highlighted box which referred to Firmagon and linked to the Firmagon copy. The agency's role in relation to the placement of the banner was unclear. The Panel was concerned about the banner. The email from the agency to the patient organisation stated 'Thanks so much for offering to put a box on your front page relating to "For more information about Firmagon, click here …"'. Thus, at the very least, the agency had been put on notice that the reference to Firmagon would appear on the front page. The Panel queried whether this, in effect, advertised Firmagon, a prescription only medicine to the public in contravention of Clause 22.1. The Panel noted that Ferring had not raised this point in its voluntary admission.

Complaint received **7 August 2009**

Case completed **17 September 2009**

CASE AUTH/2260/9/09

VOLUNTARY ADMISSION BY BOEHRINGER INGELHEIM

Conduct of representative

Boehringer Ingelheim voluntarily admitted that one of its representatives had emailed a health professional with potentially disparaging and misleading information on Bayer's product Xarelto (rivaroxaban). Xarelto and Boehringer Ingelheim's product Pradaxa (dabigatran) were both indicated for the prevention of venous thromboembolic events in adults who had undergone elective total hip or knee replacement surgery.

The action to be taken in relation to a voluntarily admission by a company was set out in of the Constitution and Procedure which stated, *inter alia*, that the Director should treat the matter as a complaint if it related to a potentially serious breach of the Code. A representative providing potentially misleading and disparaging information about a competitor product was a serious matter and the admission was accordingly treated as a complaint.

The email read:

> **'As agreed at our last meeting just a brief reminder to you about checking the average length of bed stay for June/July with Rivaroxaban patients.**
>
> **Some additional information, over in [a named town] Rivaroxaban has been removed from the formulary. The orthopods had concerns about the bleeding rates with Rivaroxaban.'**

Boehringer Ingelheim submitted that the email contravened its company policies and standard operating procedures (SOPs). The representative had been immediately suspended and subsequently dismissed. He had not maintained a high standard of ethical conduct in the discharge of his duties in breach of the Code.

The company had reminded its field force personnel of their obligations and the requirements of the Code with respect to the use of email. There would be further training on the company's SOPs.

Boehringer Ingelheim was committed to abide by the spirit and letter of the Code. This isolated incident had been taken very seriously and the company would ensure that all the necessary steps were taken to prevent such an incident being repeated.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that on 30 July the representative in question had sent twelve other emails similar to that at issue. The Panel was extremely concerned about the representative's behaviour. The emails, which should have been certified as they were promotional material, contained false information. It appeared from a later email sent by the representative that rivaroxaban had never been on the [named town] formulary. The email of 30 July was thus misleading and not capable of substantiation. Breaches of the Code were ruled as acknowledged by Boehringer Ingelheim. The information in the email related to claims regarding side effects for a competitor product. The Panel considered that the requirement in the Code that information and claims about side effects must reflect available evidence or be capable of substantiation by clinical experience applied to statements about competitor products. The Panel considered that the email was in breach and ruled accordingly. The email disparaged rivaroxaban and a breach was ruled as acknowledged by Boehringer Ingelheim. The representative had not maintained a high standard of ethical conduct or complied with all the requirements of the Code. A breach was ruled as acknowledged by Boehringer Ingelheim.

The Panel noted that on discovering the email Boehringer Ingelheim had suspended the representative in question. It was not clear how the email had come to light. The Panel was concerned about the number of emails sent. Companies were responsible for the conduct of their representatives. The Panel accepted that on discovering the problem Boehringer Ingelheim had taken action, however the fact that the representative had sent the emails in the first instance meant that high standards had not been maintained and a breach of the Code was ruled. The Panel did not consider that the circumstances amounted to a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Boehringer Ingelheim Limited voluntarily admitted that one of its representatives had emailed a consultant orthopaedic surgeon with information on Bayer's product Xarelto (rivaroxaban) which could be seen as disparaging as well as potentially misleading. Boehringer Ingelheim marketed Pradaxa (dabigatran).

Pradaxa and Xarelto were both indicated for the prevention of venous thromboembolic events in adults who had undergone elective total hip or knee replacement surgery.

The action to be taken in relation to a voluntarily admission by a company was set out in Paragraph 5.4 of the Constitution and Procedure which stated, *inter alia*, that the Director should treat the matter

as a complaint if it related to a potentially serious breach of the Code. A representative providing a health professional with potentially misleading and disparaging information about a competitor product was a serious matter and the admission was accordingly treated as a complaint.

COMPLAINT

Boehringer Ingelheim referred to an email which one of its representatives had sent to a consultant orthopaedic surgeon. The email read:

'As agreed at our last meeting just a brief reminder to you about checking the average length of bed stay for June/July with Rivaroxaban patients.

Some additional information, over in [a named town] Rivaroxaban has been removed from the formulary. The orthopods had concerns about the bleeding rates with Rivaroxaban.'

Boehringer Ingelheim submitted that the email contravened its company policies and standard operating procedures (SOPs). As a result the representative had been immediately suspended, subjected to a disciplinary hearing and subsequently dismissed.

Boehringer Ingelheim submitted that the representative had not maintained a high standard of ethical conduct in the discharge of his duties and so had breached Clauses 8.1 (disparaging), 7.2 (misleading information) and 15.2 (high standards of ethical conduct) of the Code.

The company had communicated directly with its field force personnel to remind them of their obligations and the requirements of the Code with respect to the use of email. Regional business managers would also undertake further training/briefings on the company's SOPs.

Boehringer Ingelheim submitted that it was committed to abide by the spirit and letter of the Code. This isolated incident had been taken very seriously and the company would ensure that all the necessary steps were taken to prevent such an incident being repeated.

When writing to Boehringer Ingelheim the Authority asked it to respond in relation to Clauses 2, 7.2, 7.3, 7.4, 7.9, 9.1 and 15.2.

RESPONSE

Boehringer Ingelheim stated that as set out above, the representative's conduct breached company policies and procedures and was initiated without the company's knowledge or sanction. The company was committed to maintaining the highest standard of conduct and to comply with all the requirements of the Code. It ensured that all employees were aware of these requirements and abided by them. On knowing of the unprompted action of the representative the company immediately suspended him while investigating the case and dismissed him at the conclusion of the investigation. This decisive action, together with the voluntary admission to the Authority, reflected Boehringer Ingelheim's commitment to not bring discredit to, or reduce confidence in the industry.

The information that the representative emailed to the consultant did not come from a company source, and was to Boehringer Ingelheim's knowledge not factually correct in that rivaroxaban was not removed from the [named town] formulary. The information could thus be seen as misleading and in breach of Clause 7.2. As the information could not be substantiated, the claim could potentially be in breach of Clause 7.4.

The email did not mention a brand name or make a comparison; Boehringer Ingelheim thus believed that Clause 7.3 had not been breached.

Boehringer Ingelheim had voluntarily admitted a breach of Clause 7.2 as the information that rivaroxaban had been removed from the formulary in question was incorrect and could therefore be misleading. Similarly, the reason mentioned as to why it allegedly had been taken off the formulary ('concerns over bleeding rates') could not be substantiated and Boehringer Ingelheim noted that it had admitted to a potential breach of Clause 8.1 in this regard. However, there were no claims about the safety of Boehringer Ingelheim's own product (dabigatran) and so there was no breach of Clause 7.9.

Boehringer Ingelheim accepted that the representative had not maintained a high standard of ethical conduct in the discharge of his duties and that his conduct amounted to a breach of Clause 15.2. Boehringer Ingelheim did not tolerate the representative's behaviour as evidenced by his dismissal. However, Boehringer Ingelheim believed that the rogue activity of this one representative did not reflect a failure of the company to maintain high standards and there was no breach of Clause 9.1.

During the meeting referred to in the email, held on 22 June to discuss the consultant's recent attendance at a conference, the consultant referred to the differences in length of bed stays between certain clinical trials. The consultant asked the representative to email him in early August to remind him to review the length of bed stays in June and July.

Boehringer Ingelheim did not believe that any materials had been used by the representative or that he had acted on any briefing materials.

It was not Boehringer Ingelheim's understanding that rivaroxaban had been removed from the formulary in question. The company did not issue or sanction any communication regarding this matter. The representative had acted on knowledge obtained through his own network of contacts. Boehringer Ingelheim emphasised that the

representative did not disclose the email either before or after it was sent. The representative did not follow internal SOPs and the email was not certified in accordance with Clause 14.1.

In completing the internal investigation of this case, Boehringer Ingelheim had uncovered similar emails sent by the representative to other customers, unprompted by and undisclosed to the company. Copies were provided.

PANEL RULING

The Panel noted that on 30 July the representative in question had sent twelve other emails similar to that at issue. The Panel was extremely concerned about the representative's behaviour. The emails, which should have been subject to the certification process as they were promotional material, contained false information. It appeared from an email sent by the representative on 5 August that rivaroxaban had never been on the [named town] formulary. The email of 30 July was thus misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled as acknowledged by Boehringer Ingelheim. The email was not a comparison and thus no breach of Clause 7.3 was ruled. The information in the email related to claims regarding side effects for a competitor product. The Panel considered that Clause 7.9 was not limited to claims about a company's own product. The requirement that information and claims about side effects must reflect available evidence or be capable of substantiation by clinical experience applied to statements about competitor products. The Panel considered that the email was in breach of Clause 7.9 and ruled accordingly. The email disparaged rivaroxaban and a breach of Clause 8.1 was ruled as acknowledged by Boehringer Ingelheim. The representative had not maintained a high standard of ethical conduct or complied with all the requirements of the Code. A breach of Clause 15.2 was ruled as acknowledged by Boehringer Ingelheim.

The Panel noted that on discovering the email Boehringer Ingelheim had suspended the representative in question. It was not clear how the email had come to light. The Panel was concerned about the number of emails sent. Companies were responsible for the conduct of their representatives. The Panel accepted that on discovering the problem Boehringer Ingelheim had taken action, however the fact that the representative had sent the emails in the first instance meant that high standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances amounted to a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Complaint received **1 September 2009**

Case completed **1 October 2009**

CASE AUTH/2261/9/09

VOLUNTARY ADMISSION BY MERCK SHARP & DOHME

Breach of undertaking

Merck Sharp & Dohme voluntarily admitted that it might have breached its undertaking given in Case AUTH/2212/3/09 in that an electronic banner advertisement for Cozaar (losartan) had appeared in MIMS Monthly Update issued on 1 September. The banner advertisement featured a claim similar to that which had previously been ruled in breach of the Code (Case AUTH/2212/3/09). Cozaar was an angiotensin II antagonist (AIIA).

The action to be taken in relation to a voluntary admission by a company was set out in Paragraph 5.4 of the Constitution and Procedure which stated, *inter alia*, that the Director should treat the matter as a complaint if it related to a potentially serious breach of the Code. The breach of an undertaking was a serious matter and the admission was accordingly treated as a complaint.

The detailed response from Merck Sharp & Dohme is given below.

The Panel noted that in Case AUTH/2212/3/09 the claim 'there are no clinically meaningful BP [blood pressure] lowering differences between available [AIIAs]' was ruled to be misleading in breach of the Code. The publisher of MIMS monthly update had been clearly instructed by Merck Sharp & Dohme to 'pull all the Cozaar digital advertisements that are live at the latest by tomorrow [12 June] from any of your websites. We have had a complaint … which has been upheld by the code. Tomorrow is the deadline for these to be taken down'. Updated advertisements were to be provided. The publisher confirmed by email on 11 June that '… all copies of the advert have been deleted from our servers'. Following publication of the advertisement on 1 September the publisher confirmed that one of its employees had retained a copy on their own computer and this was used in error. The publisher had informed staff of its change in policy so that, without exception, advertisements were only stored on one server. The publisher stated that the advertisement appeared because of its error and Merck Sharp & Dohme had done everything in its power to ensure the advertisement did not reappear.

The Panel noted that the advertisement now at issue (Case AUTH/2261/9/09) included the claim 'Evidence from a new independent review by the Cochrane collaboration suggests that there are no clinically meaningful BP lowering differences between available AIIAs'. This was sufficiently similar to the claim at issue in Case AUTH/2212/3/09 for it to be covered by the undertaking given in that case.

The Panel considered that Merck Sharp & Dohme had taken all possible steps to comply with its undertaking and that it had been very badly let down by the publisher. The Panel had no option but to rule a breach of the Code as the publisher's failure to comply with the instructions meant that Merck Sharp & Dohme had breached its undertaking. In the circumstances the Panel did not consider that Merck Sharp & Dohme had failed to maintain high standards or that it had brought discredit upon, or reduced confidence in, the industry. Thus no breaches of the Code, including Clause 2 and were ruled.

Merck Sharp & Dohme Limited voluntarily admitted that it might have breached its undertaking given in Case AUTH/2212/3/09 in that an electronic banner advertisement for Cozaar (losartan) (ref 04-10CZR.09.GB.10269.AV) had appeared in MIMS Monthly Update issued on 1 September. The banner advertisement featured a claim similar to that which had previously been ruled in breach of the Code. Cozaar was an angiotensin II antagonist (AIIA).

The action to be taken in relation to a voluntary admission by a company was set out in Paragraph 5.4 of the Constitution and Procedure which stated, *inter alia*, that the Director should treat the matter as a complaint if it related to a potentially serious breach of the Code. The breach of an undertaking was a serious matter and the admission was accordingly treated as a complaint.

COMPLAINT

Merck Sharp & Dohme noted that Case AUTH/2212/3/09 concerned a complaint about the claim 'A new independent Cochrane review suggests that 'there are no clinically meaningful BP lowering differences between available [AIIAs]" in promotional material for Cozaar. The Appeal Board ruled that the claim was misleading and Merck Sharp & Dohme signed and returned the form of undertaking on 12 June 2009.

After the unsuccessful appeal on 21 May, Merck Sharp & Dohme wrote to all advertisers, including the publisher of MIMS Monthly Update, to notify them of the withdrawal of affected advertisements. At that time an electronic banner was the only Cozaar advertisement in use by the publisher. Withdrawal of this item was requested because it included the claim 'Evidence from a new independent review by the Cochrane collaboration suggests that there are no clinically meaningful BP lowering differences between available AIIAs.'

Merck Sharp & Dohme wrote to the publisher on

the 11 June to ask that it withdraw the banner advertisement from use because of a Code breach, and confirm that the file had been destroyed. The publisher replied the same day to confirm that the banner had been withdrawn and that all file copies of the artwork had been destroyed. A copy of the correspondence was provided.

Merck Sharp & Dohme noted that the Cozaar banner advertisement in question was included in the electronic MIMS Monthly Update, issued on 1 September. Merck Sharp & Dohme understood that the update had been circulated to several thousand health professionals.

Merck Sharp & Dohme had since asked the publisher to ensure that it had destroyed the Cozaar banner advertisement and to investigate how the withdrawn advertisement, allegedly deleted from its archives, had appeared in one of its publications. The publisher had submitted that although the electronic file was destroyed from its central archive, it had been held as a local copy by one of its employees who then used it in the September edition of MIMS Monthly Update. This additional copy had been deleted and steps taken to ensure that there was only ever one copy of all materials in the central archive and that no local copies were made and retained by staff.

The publisher had apologised and accepted full responsibility for the error; it had stated that there was nothing additional that Merck Sharp & Dohme could have done to avoid this problem. A copy of the relevant correspondence was provided.

Merck Sharp & Dohme submitted that it had informed Takeda UK Limited, the complainant in Case AUTH/2212/3/09, of this error.

Merck Sharp & Dohme noted that the Constitution and Procedure (Paragraph 5.4) provided that the Director should treat an admission as a complaint if it related to a potentially serious breach of the Code or if the company failed to take appropriate action to address the matter. Merck Sharp & Dohme considered that it had provided evidence that it took all reasonable steps and appropriate actions to prevent re-use of this withdrawn advertisement (the company asked the publisher to delete all copy, explained the reason why and was specifically notified that the advertisement had been destroyed). Accordingly, Merck Sharp & Dohme hoped that the Director would use the discretion provided by Paragraph 5.4 to decide not to treat this admission as a prima facie complaint and thus a potential breach of Clause 25 of the Code.

Merck Sharp & Dohme submitted that it remained committed to the Code and fully supported the importance of any undertaking it gave following a ruling of a breach. The company was very concerned to discover that, despite its procedures which were adhered to fully by its staff, there were errors at a major medical publisher which caused this unfortunate situation. Nevertheless, Merck Sharp & Dohme was heartened by the fact that, as a result, the publisher had changed its internal procedures to prevent such an occurrence happening again. This would benefit the UK industry and all companies that had a UK presence.

When writing to Merck Sharp & Dohme the Authority asked it to respond in relation to Clauses 2, 9.1 and 25 of the Code.

RESPONSE

Merck Sharp & Dohme stated that the banner advertisement in question was included in MIMS Monthly Update emailed to recipients on 1 September 2009. Although it did not include the claim previously found in breach by the Appeal Board, it was sufficiently similar to warrant its withdrawal. Merck Sharp & Dohme identified the error in this advertisement on 3 September 2009 and immediately investigated and discovered that the publisher had made a mistake.

The detailed facts were as follows:

- 11 June 2009. Following receipt of the Appeal Board's ruling in Case AUTH/2212/3/09, Merck Sharp & Dohme told the publisher that the banner advertisement was effectively in breach of the Code and should be withdrawn. Further, Merck Sharp & Dohme requested that the item should be deleted from the publisher's electronic files and requested confirmation. The publisher subsequently confirmed that the advertisement had been withdrawn and that the electronic files had been deleted.
- 12 June 2009. Merck Sharp & Dohme returned its undertaking to comply with the Appeal Board's ruling.
- July and August 2009. The correct replacement Cozaar banner advertisement was hosted by the publisher on its medical websites.
- 3 September 2009. Merck Sharp & Dohme noted that the September edition of MIMS Monthly Update contained a copy of the advertisement at issue. Investigations were initiated by telephone and email. The publisher, confirmed the deletion of the advertisement from its central files, but discovered that an individual employee had retained a copy on their own computer and accidentally used it instead of the correct advertisement. Merck Sharp & Dohme telephoned the Director, informing her of the situation. The Director advised a written voluntary admission. Takeda, was told about the situation and that Merck Sharp & Dohme would make a voluntary admission.
- 4 September 2009. A formal letter of apology was received from the publisher confirming the facts described above. The letter formally concluded that the error was wholly the responsibility of the publisher and that no blame lay with Merck Sharp & Dohme. A letter containing all of the facts was sent to Authority.

Merck Sharp & Dohme submitted that Cases AUTH/2192/12/08; AUTH/1866/7/06; AUTH/2048/9/07;

AUTH/2049/9/07 and AUTH/2050/9/07; recent voluntary admission cases were relevant to the current case.

Merck Sharp & Dohme gave a brief overview of what it considered important factors leading to the rulings in those cases. It submitted, *inter alia*, that in Case AUTH/2192/12/08, the Appeal Board had ruled no breach of Clause 25 of the Code as well as no breach of Clause 2.

In this current case, Case AUTH/2261/9/09, Merck Sharp & Dohme received written confirmation from the publisher that the advertisement in breach would be withdrawn from further use and that existing copy would be deleted. In addition, Merck Sharp & Dohme informed the publisher of the Code breach as the reason for withdrawal and deletion of the advertisement as referred to in Cases AUTH/2192/12/08 and AUTH/2048/9/07.

Merck Sharp & Dohme believed that its actions in connection with the withdrawal of its advertisement met the criteria used by the Appeal Board in Case AUTH/2192/12/08, including informing the publisher about the breach of the Code which the Appeal Board had considered might have been 'helpful'. Furthermore, in the previous cases breaches were ruled because the companies had failed to do things which Merck Sharp & Dohme did do in this case.

Merck Sharp & Dohme regretted very deeply that this incident has occurred. An undertaking made to the PMCPA was always taken very seriously and would never knowingly be broken. In this case, however, Merck Sharp & Dohme considered that it had done its utmost to meet those obligations.

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 Merck Sharp & Dohme was wrong in its submission that in Case AUTH/2192/12/08 no breach of Clause 25 was ruled. In Case AUTH/2192/12/08 the respondent company was ruled in breach of Clause 25 for failing to comply with an undertaking. No breach of Clauses 2 and 9.1 was ruled in that case.

The Panel noted that in Case AUTH/2212/3/09 the claim 'there are no clinically meaningful BP [blood pressure] lowering differences between available [AIIAs]' in promotional material for Cozaar was ruled to be misleading in breach of Clauses 7.2 and 7.3 of the Code. The publisher had been clearly instructed by Merck Sharp & Dohme to 'pull all the Cozaar digital advertisements that are live at the latest by tomorrow [12 June] from any of your websites. We have had a complaint … which has been upheld by the code. Tomorrow is the deadline for these to be taken down'. Updated advertisements were to be provided. The publisher confirmed by email on 11 June that '… all copies of the advert have been deleted from our servers'. Following publication of the advertisement on 1 September the publisher confirmed that one of its employees had retained a copy on their own computer and this was used in error. The publisher had changed its policy so that, without exception, advertisements were only stored on one server. Staff had been informed. The publisher stated that the advertisement appeared because of its error and Merck Sharp & Dohme had done everything in its power to ensure the advertisement did not reappear.

The Panel noted that the advertisement now at issue (Case AUTH/2261/9/09) included the claim 'Evidence from a new independent review by the Cochrane collaboration suggests that there are no clinically meaningful BP lowering differences between available AIIAs'. This was sufficiently similar to the claim at issue in the previous case, Case AUTH/2212/3/09, for it to be covered by the undertaking given in that case.

The Panel considered that Merck Sharp & Dohme had taken all possible steps to comply with its undertaking and that it had been very badly let down by the publisher. The Panel had no option but to rule a breach of Clause 25 as the publisher's failure to comply with the instructions meant that Merck Sharp & Dohme had breached its undertaking. In the circumstances the Panel did not consider that Merck Sharp & Dohme had failed to maintain high standards or that it had brought discredit upon, or reduced confidence in, the industry. Thus no breach of Clauses 2 and 9.1 were ruled.

Complaint received **4 September 2009**

Case completed **7 October 2009**

CASE AUTH/2263/9/09

BRISTOL-MYERS SQUIBB v BOEHRINGER INGELHEIM

Viramune journal advertisement

Bristol-Myers Squibb complained about a journal advertisement for Viramune (nevirapine) placed by Boehringer Ingelheim in HIV Medicine, July 2009. Viramune was indicated in combination with other anti-retroviral medicines for the treatment of HIV-1 infected adults, adolescents and children. The recommended dose of Viramune in patients aged 16 years or over was 200mg daily for the first two weeks followed by 200mg twice daily thereafter.

The advertisement stated 'Have you heard?' Followed by 'New Viramune data will be coming soon'. Subsequent text referred to the ArTEN study and briefly described the treatment regimens used. No doses were stated. The text concluded with 'With results expected soon, you will have more reasons than ever to talk about Viramune'. Bristol-Myers Squibb considered that the advertisement encouraged readers to review the results of the ArTEN study when they became available.

Bristol-Myers Squibb noted that ArTEN included, *inter alia*, two Viramune treatment arms, 200mg twice daily (licensed dose) or 400mg once daily (unlicensed dose), each combined with Truvada. As Viramune was not licensed for once daily use, Bristol-Myers Squibb alleged that the advertisement was not in accordance with the Viramune marketing authorization.

Bristol-Myers Squibb also alleged that the advertisement was a 'teaser' in that it elicited an interest in the study's results which would follow without actually providing any information about them.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that from the overview of the ArTEN study published in 2009 (Soriano and de Rossi), it was clear that some patients would be randomised to receive Viramune 400mg once daily. The study had commenced in 2006 and the results on the primary endpoint were expected during the first quarter of 2009. The first presentation of the results was scheduled for July 2009. Regular safety reviews had been held. There was no indication in the overview as to whether a separate analysis would be made of the once daily/twice daily dosing of Viramune.

The advertisement drew attention to the ArTEN study trial and would encourage health professionals to look at the trial outcome. The Panel noted that the advertisement had been withdrawn before the publication of the ArTEN results. The advertisement did not refer to any dose of Viramune but it elicited interest in the results of the study. The Panel considered it immaterial that the advertisement did not refer to any results. Merely raising awareness of a specific study would draw attention to it. By noting within the advertisement that the results would soon be available the Panel considered that Boehringer Ingelheim had in effect advertised the outcome of that study. Thus all outcomes would have to be in accordance with the Code and not relate to unlicensed doses. There was a difference between using data from a study which included licensed and unlicensed doses to substantiate a specific, within licence claim, and general use for promotional purposes of a study that used licensed and unlicensed doses.

The Panel considered that given the inclusion of an unlicensed dosing regimen in the ArTEN study the advertisement in effect constituted promotion that was inconsistent with the particulars listed in the Viramune SPC. A breach of the Code was ruled.

The Panel did not consider the advertisement was a teaser as set out in the supplementary information to the Code. Information about Viramune had been provided, including prescribing information.

Bristol-Myers Squibb Pharmaceuticals Limited complained about a journal advertisement (ref NVP3846) for Viramune (nevirapine) placed by Boehringer Ingelheim Limited in HIV Medicine, July 2009. Inter-company correspondence had failed to resolve the matter.

Viramune was indicated in combination with other anti-retroviral medicines for the treatment of HIV-1 infected adults, adolescents and children. The dose of Viramune in children was dependent upon body surface area or body weight. In patients aged 16 years or over the recommended dose was 200mg daily for the first two weeks followed by 200mg twice daily thereafter.

The advertisement stated 'Have you heard?' Followed by 'New Viramune data will be coming soon'. Subsequent text explained that the ArTEN study compared Viramune with atazanavir (Bristol-Myers Squibb's product Reyataz) boosted with ritonavir (Abbott Laboratories' product, Norvir) and on a background of Truvada (fixed dose tenofovir and emtricitabine) (Gilead Sciences' product) in treatment naïve patients. The text concluded with 'With results expected soon, you will have more reasons than ever to talk about Viramune'.

COMPLAINT

Bristol-Myers Squibb considered that the

advertisement encouraged readers to review the results of the ArTEN study when they became available.

Viramune was licensed to be taken twice daily. ArTEN compared atazanavir/ritonavir once daily vs Viramune 200mg twice daily (licensed dose) or 400mg once daily (unlicensed dose), each combined with Truvada. As Viramune did not have a licence for once daily use, Bristol-Myers Squibb alleged that the advertisement was not in accordance with the Viramune marketing authorization in breach of Clause 3.2 of the Code.

In inter-company dialogue Boehringer Ingelheim had acknowledged that once daily Viramune did not have marketing authorization but stated that it was not promoting outside the marketing authorization as no direct reference was made to the once daily information. Boehringer Ingelheim had omitted to state that 188 out of the 376 patients were recruited to the once daily Viramune arm and that these patients contributed to the primary endpoint.

Bristol-Myers Squibb also alleged that the advertisement was a 'teaser' in that it elicited an interest in the study's results which would follow without actually providing any information about them.

In inter-company dialogue Boehringer Ingelheim had stated that the description of patient numbers and treatment groups was sufficient for the advertisement not to be considered a teaser. However, the statements 'Have you heard' and 'results expected soon' suggested that the intent was to advertise that the study results would shortly be available, rather than purely to advertise the data stated within it. Bristol-Myers Squibb alleged a breach of Clause 9.1.

RESPONSE

Boehringer Ingelheim stated that the advertisement at issue was used before the ArTEN data was presented at the 5th International Aids Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention, 19-22 July 2009 and was therefore no longer in use.

The ArTEN study compared three treatment arms: atazanavir/ritonavir once daily, Viramune 200mg twice daily (licensed dose), Viramune 400mg once daily (unlicensed dose). Viramune was combined with Truvada.

The advertisement contained a factual description of the number and type of HIV patients and the treatments used in the study (Viramune and Truvada). It also stated that new results from the study would be available soon. In addition, it included the Viramune brand name, the Viramune ArTEN study name and the prescribing information. The advertisement did not refer to once daily (unlicensed) dosing of Viramune.

As the advertisement notified readers of future data from the ArTEN trial and was used before the IAS Conference, 19 - 22 July 2009, the recruitment data and the contribution of the arms of the study to the primary endpoint would not have been confirmed until presentation of the ArTEN results at the conference. Boehringer Ingelheim therefore believed that it was unfair for Bristol-Myers Squibb to state that 'Boehringer Ingelheim had omitted to state that 188 out of the 376 patients were recruited to the once daily Viramune arm and that these patients contributed to the primary endpoint'. Bristol-Myers Squibb had raised a point that it now knew only to be true after the data had been presented and after the advertisement had been withdrawn.

Whilst Boehringer Ingelheim agreed that Viramune was not licensed for once daily dosing it refuted the suggestion that the advertisement promoted Viramune outside its marketing authorization. Boehringer Ingelheim therefore denied a breach of Clause 3.2.

Boehringer Ingelheim understood that the Code did not preclude the use, in promotion, of data from clinical trials where licensed and unlicensed treatment regimens were included. However, only the data for licensed dosing regimens could be used in promotional material to substantiate claims. Boehringer Ingelheim therefore believed that the ArTEN study could be used in promotion in an appropriate manner. It also believed that the advertisement at issue was an appropriate use of the ArTEN study for the promotion of Viramune.

Boehringer Ingelheim refuted the suggestion that high standards had not been maintained in breach of Clause 9.1. A 'teaser' advertisement was one that elicited an interest in something without providing any information about it. The advertisement clearly provided information about the ArTEN study (factual description of the estimated numbers and type of HIV patients that entered the study and the basic treatment groups evaluated) and a statement that data from the study would be available in the future.

Boehringer Ingelheim understood that the Code did not require that the information provided be about the results as Bristol-Myers Squibb stated in its complaint. Boehringer Ingelheim equally believed that the advertisement did not contain any language to encourage readers to review specifically the results of the study as opposed to the study in its entirety.

Boehringer Ingelheim believed that the advertisement was an appropriate method of increasing clinicians' awareness of an important clinical trial before the results were presented. The ArTEN study provided new important toxicity and safety information for health professionals treating HIV with commonly used treatment regimens under specific therapeutic guidance:

- The European Medicines Evaluation Agency's scientific committee, the Committee for Proprietary Medicinal Products (CPMP) added important CD4+ guidance concerning patient management and risk factors for hepatic and rash reactions to the Viramune summary of product characteristics (SPC) (4 February 2004) which stated that nevirapine should be used only in men <400 cells/mm3; women <250 cells/mm3 unless the benefit outweighed the risk.
- Unlike previous studies, patients enrolled in the ArTEN study had CD4+ cell counts as recommended within the CD4+ guidelines for nevirapine use (men <400 cells/mm3; women <250 cells/mm3). Previous studies had included patients with higher CD4+ counts and thus this was the first study to prospectively evaluate the efficacy and safety of nevirapine use within the CD4+ count guidelines.
- The combination of tenofovir and emtricitabine [Truvada] was recommended as one of the first line treatment options in all major guidelines, and was widely used. It was therefore a treatment option that physicians were likely to consider. ArTEN was the first large study to examine the efficacy and safety of nevirapine in combination with tenofovir and emtricitabine; smaller studies had provided conflicting results.

Since this advertisement clearly provided information about the ArTEN study (ie patient numbers, treatment groups) it therefore, by definition, could not be considered as a 'teaser' advertisement and so did not breach Clause 9.1.

The Authority had requested a copy of the information that would be supplied to a health professional who contacted Boehringer Ingelheim. All responses for further information to this advertisement would be referred to medical information and the response would depend on the specific information being requested. Whilst the advertisement was being used Boehringer Ingelheim would have only been able to respond on request to provide details of the clinical trial design and/or the date when the ArTEN data would be presented.

In response to a request for further information Boehringer Ingelheim stated that the information that was in the public domain about the ArTEN study when the advertisement was published would have been that presented on www.clinicaltrials.gov. In addition, an overview of the ArTEN trail had been published (Soriano and de Rossi, 2009).

The information now in the public domain about the ArTEN study consisted of two poster presentations, one from the IAS Congress, July 2009 (Soriano *et al*) and the other from the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 2009 (Johnson *et al*).

In response to the Panel's request for a copy of the further information that would now be supplied to a health professional who contacted Boehringer Ingelheim, the company stated that all requests for further information to the advertisement would be referred to medical information; the response would depend on the specific information requested. Medical information would contact the enquirer to ask which specific information relating to ArTEN was required. If the enquirer requested information on the study design the letter entitled 'ArTEN study design information request' would be provided. If the enquirer specifically requested the data presented on ArTEN to date, then the letter entitled 'request for ArTEN data' would be provided along with the poster publications.

PANEL RULING

The Panel noted that from the overview of the ArTEN study published in 2009 (Soriano and de Rossi), it was clear that some patients would be randomised to receive Viramune 400mg once daily. The study had commenced in 2006 and the results on the primary endpoint were expected during the first quarter of 2009. The first presentation of the results was scheduled for July 2009. Regular safety reviews had been held. There was no indication in the overview as to whether a separate analysis would be made of the once daily/twice daily dosing of Viramune.

The advertisement drew attention to the ArTEN study and would encourage health professionals to look at the outcome. The Panel noted that Boehringer Ingelheim had withdrawn the advertisement before the publication of the ArTEN results. The Panel did not consider that this meant that the advertisement could not be in breach of the Code. The advertisement did not refer to any dose of Viramune but it elicited interest in the results of the study. The Panel considered it immaterial that the advertisement did not refer to any results. Merely raising awareness of a specific study would draw attention to it. By noting within the advertisement that the results would soon be available the Panel considered that Boehringer Ingelheim had in effect advertised the outcome of that study. Thus all outcomes would have to be in accordance with the Code and not relate to unlicensed doses. There was a difference between using data from a study which included licensed and unlicensed doses to substantiate a specific, within licence claim, and general use for promotional purposes of a study that used licensed and unlicensed doses.

The Panel considered that given the inclusion of an unlicensed dosing regimen in the ArTEN study the advertisement in effect constituted promotion that was inconsistent with the particulars listed in the Viramune SPC. A breach of Clause 3.2 was ruled.

The Panel did not consider the advertisement was a teaser as set out in the supplementary information to Clause 9.1. Information about

Viramune had been provided, including prescribing information, and thus the Panel ruled no breach.

During its consideration of this case the Panel noted that in its view any requests for information about the ArTEN study generated by the advertisement could not be considered unsolicited. This meant that responding to such requests could not take the benefit of the exemption to Clause 1.2 as set out in the supplementary information to that clause. The Panel requested that Boehringer Ingelheim be advised of its views in this regard.

Complaint received **9 September 2009**

Case completed **27 October 2009**

CASE AUTH/2264/9/09

ANONYMOUS v GLAXOSMITHKLINE

Invitation to a satellite symposium

An anonymous and uncontactable complainant, complained about an invitation from GlaxoSmithKline to a satellite symposium entitled 'Living with PAH [pulmonary arterial hypertension] – Challenges and Options' at the European Society of Cardiology (ESC) Congress in Barcelona 2009.

The complainant alleged that the symposium promoted Flolan (epoprostenol) and Volibris (ambrisentan) (both marketed by GlaxoSmithKline). In fact the third talk was simply full of Volibris data. The complainant alleged that it was disguised promotion; the invitation, from which it appeared that the symposium was about PAH as a disease, should have made clear that talks contained product information so he could decide not to attend. The complainant further noted that prescribing information was missing from the invitation, there was no date and the colours of the invitation were the same as the Volibris logo.

The detailed response from GlaxoSmithKline is given below.

The Panel noted that the invitation to the symposium, which had been freely available for delegates to pick up from GlaxoSmithKline's exhibition stand, clearly stated that the event was sponsored by GlaxoSmithKline and a brief description referred to a presentation of the latest data regarding long-term treatment with ambrisentan. The invitation included the agenda and listed the third presentation 'Long-term Treatment with Ambrisentan: FCII and CTD'. In the Panel's view, it was clear from the invitation that the symposium would include information about treatment options, including Volibris. The Panel did not consider that the symposium was disguised promotion. No breach of the Code was ruled.

The Panel considered that as the invitation referred to ambrisentan and its use in PAH it was, in effect, promotional material for Volibris and in that regard it should have included prescribing information; as it did not a breach of the Code was ruled.

The complainant had stated, *inter alia*, that there was no date on the invitation by which the Panel assumed that he meant that there was no date of preparation. The Code required all promotional material other than advertisements appearing in professional publications to include the date on which the material was drawn up or last revised. Thus, in the Panel's view, the invitation should have included a 'date of preparation'. GlaxoSmithKline had not been asked to respond in relation to the requirements of the relevant clause, Clause 4.10 and so the Panel could make no ruling in that regard. The Panel requested that the company be advised of its view.

An anonymous and uncontactable complainant, writing as an 'Unhappy Physician', complained about an invitation (ref P/03/09/190) from GlaxoSmithKline (UK) Limited to a satellite symposium.

COMPLAINT

The complainant explained that he had attended this year's European Society of Cardiology (ESC) Congress in Barcelona where he was handed an invitation to a symposium entitled 'Living with PAH [pulmonary arterial hypertension] – Challenges and Options'. The complainant was interested and so decided to learn more about the disease.

When the complainant sat down it became clear that the symposium promoted Flolan (epoprostenol) and Volibris (ambrisentan) (both marketed by GlaxoSmithKline). Had the complainant known this at the outset he would not have attended as it seemed from the invitation to be a symposium about the disease. In fact the third talk was simply full of Volibris data.

The complainant was still angry at the way this symposium was advertised; he alleged that it was disguised promotion. The complainant had discussed this issue with a fellow physician who worked for the industry and it seemed that the invitation should have made clear that talks contained product information so he could decide not to attend. The fellow physician also mentioned that other elements were missing from the invitation such as 'prescription information' which, apparently, implied its promotional nature as products were directly mentioned. The complainant noted that the colours of the invitation were the same as the Volibris logo and there was no date on the invitation.

The complainant hoped his complaint was taken seriously and future advertising was clearer as he had better things to do with an hour of his time than sit in industry symposia being sold to.

When writing to GlaxoSmithKline the Authority asked it to respond in relation to Clauses 2, 4.1, 9.1 and 12.1 of the Code and to note the requirements of Clause 1.7 and its supplementary information referring to the applicability of codes.

RESPONSE

GlaxoSmithKline regretted the disappointment felt

by the complainant and took the issues raised very seriously. GlaxoSmithKline noted that an industry physician had advised the complainant about the specific matters to raise.

GlaxoSmithKline stated that the symposium at issue was organised by its European Critical Diseases Business Unit, a pan-European group that operated at an above country level and was made up of medical and marketing staff. Invitations to the symposium were freely available on the GlaxoSmithKline conference exhibition stand for delegates to pick up and attend if they wished. GlaxoSmithKline did not take a note of the estimated 175 symposium attendees. The ESC meeting was the world's biggest international meeting in cardiology with over 30,000 delegates. The nationality of attendees at the symposium was likely to reflect the make-up of the delegates in general.

The invitation, abstract booklet, symposium banners and question cards all clearly stated that the symposium was organised by GlaxoSmithKline. The biographies and abstracts booklet were provided to each attendee in the meeting by being placed on every seat as well as being available at the entrance to the meeting room. The booklet contained declarations of GlaxoSmithKline's involvement with the symposium as well as the prescribing information. Whilst the symposium was organised and arranged by GlaxoSmithKline and therefore required full review under the relevant codes of practice, such symposia were also platforms for legitimate exchange of scientific information and clinicians valued their content.

GlaxoSmithKline submitted that all efforts were made to ensure that those reading the invitation would know that the symposium would contain information about ambrisentan. The third talk listed on the invitation was entitled 'Long-Term Treatment with Ambrisentan: FCII and CTD'. It thus should not have been a surprise that this talk contained Volibris data. All attendees would have received the abstract booklet before the symposium started which made clear that ambrisentan data was going to be discussed. Therefore the complainant had two opportunities to understand the nature of the meeting and decide then whether to attend.

GlaxoSmithKline understood why the complainant thought the invitation should include prescribing information but noted that it simply presented the titles of the meeting together with a message from the Chairman; there were no claims or any other information. However, the abstract book, which contained summaries of the symposium presentations, did provide prescribing information. The omission of the prescribing information from the invitation would not mislead a symposium attendee as to the information to be discussed at the meeting.

The meeting was held in Barcelona and was reviewed and approved by the central team and, under Spanish regulations, by GlaxoSmithKline's Spanish medical department.

The symposium slides were provided as requested. GlaxoSmithKline submitted that the presentations represented a fair and balanced view of the 'Challenges and Options' of living with PAH.

The complainant inferred that the symposium contained little other than Flolan and Volibris data. GlaxoSmithKline stated that the slide set only referred to the generic names of the medicine, not the brand names and the speakers only mentioned the generic names of all the medicines. Many medicines were mentioned in all talks.

The third talk entitled 'Long-Term Treatment with Ambrisentan' contained many references to ambrisentan as would be expected. Three out of the twenty-three slides explained the adverse event data. GlaxoSmithKline submitted that the ESC Congress in Barcelona was the first European meeting since the European launch of ambrisentan and therefore data about its place in PAH management and its risks and benefits would be relevant to the majority of attendees.

GlaxoSmithKline stated that although it regretted that a health professional was disappointed by the invitation and the meeting itself, the company had acted in a responsible manner: sponsorship of the symposium was clear; topics to be discussed were clear on the invitation; prescribing information was provided as appropriate. GlaxoSmithKline's intent was to arrange a meeting where speakers would present valuable information, and when presenting data on GlaxoSmithKline medicines, to ensure that this was presented transparently and with fair balance. GlaxoSmithKline submitted that it was in line with its intentions.

GlaxoSmithKline stated that this was a highly valuable symposium organised to benefit many congress delegates from across Europe. This included delegates who would have been interested in reviewing recent ambrisentan data. GlaxoSmithKline also believed that in organising this symposium it had adhered to the ABPI Code and other relevant national codes.

GlaxoSmithKline submitted that the meeting was not disguised promotion and thus not in breach of Clause 12.1. GlaxoSmithKline had complied with the relevant codes and standards, maintained high standards and had not brought the industry into disrepute and therefore, was not in breach of Clauses 1.7, 9.1 or 2.

GlaxoSmithKline provided confidential copies of the speaker slides the speaker agreements.

In response to a request for further information GlaxoSmithKline stated that the company's presence and activities at the Barcelona meeting were subject to, and approved under both the UK and Spanish Codes as described in the

supplementary information to Clause 1.7. The European Critical Disease Business Unit head office was based in the UK and the local operating companies were located in their respective European countries.

GlaxoSmithKline confirmed that all relevant materials were reviewed in accordance with the UK Code.

PANEL RULING

The Panel noted that GlaxoSmithKline had sponsored a satellite symposium at the ESC meeting in Barcelona which it had approved under both the UK and Spanish Codes.

The Panel first had to consider whether or not the UK Code applied. The symposium was organised from the UK and arrangements were also made to ensure compliance with the Spanish Code of Practice. It was clear from the supplementary information to Clause 1.7 that because the symposium was organised from the UK and held in Spain, both the UK and Spanish Codes applied.

The Panel noted that the invitation to the symposium had been freely available for delegates to pick up from GlaxoSmithKline's exhibition stand. The invitation clearly stated that the symposium was sponsored by GlaxoSmithKline and a brief description of the event referred to a presentation of the latest data regarding long-term treatment with ambrisentan. The invitation included the agenda and listed the third presentation 'Long-term Treatment with Ambrisentan: FCII and CTD'. In the Panel's view, it was clear from the invitation that the symposium would include information about treatment options, including Volibris. Thus the Panel did not consider that the symposium was disguised promotion. No breach of Clause 12.1 was ruled.

The Panel noted that the invitation referred to ambrisentan and its use in PAH. The Panel thus considered that the invitation was, in effect, promotional material for Volibris and in that regard it should have included prescribing information; as it did not a breach of Clause 4.1 was ruled.

The Panel noted its ruling above of a breach of Clause 4.1 but nonetheless did not consider that it meant that high standards had not been maintained. The Panel did not consider that the circumstances warranted ruling a breach of Clause 2 which was used as a sign of particular censure and reserved for such.

The Panel noted that the complainant had stated, *inter alia*, that there was no date on the invitation by which it assumed that the complainant meant that there was no date of preparation on the material given that it bore the date of the symposium. Clause 4.10 required that all promotional material other than advertisements appearing in professional publications must include the date on which the material was drawn up or last revised. Thus, in the Panel's view, the invitation should have included a 'date of preparation' or similar which it did not. The Authority, however, had not asked GlaxoSmithKline to respond in relation to the requirements of Clause 4.10 and so the Panel could make no ruling in that regard. The Panel requested that the GlaxoSmithKline be advised of its view.

Complaint received **10 September 2009**

Case completed **22 October 2009**

CASE AUTH/2268/9/09

CEPHALON/DIRECTOR v PROSTRAKAN

Promotion of Abstral

Cephalon alleged that an Abstral (sublingual fentanyl citrate) advertisement issued by ProStrakan which appeared in the BMJ 12 September 2009 was in breach not only of the undertaking given in Case AUTH/2207/2/09, but also in breach of that given in Case AUTH/2235/5/09.

As the complaint alleged a breach of the undertakings given in Cases AUTH/2207/2/09 and AUTH/2235/5/09 it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

Cephalon stated that it had a serious concern relating to Case AUTH/2235/5/09, in which materials were ruled to be in breach of the undertaking given in Case AUTH/2207/2/09. In Case AUTH/2235/5/09 the Panel ruled a breach of Clause 2 and had reported ProStrakan to the Code of Practice Appeal Board.

Cephalon alleged that unfortunately, the advertisement that had been part of the re-issued campaign in Case AUTH/2235/5/09 had been re published in the BMJ.

Cephalon was told about the ruling in Case AUTH/2235/5/09 on 23 June 2009. It appeared that ProStrakan had failed to ensure that all materials were withdrawn as required by the undertaking. Sufficient time had elapsed to allow ProStrakan to halt any printing of previously purchased advertising space in the BMJ.

The detailed response from ProStrakan is given below.

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/2207/2/09 the claim at issue, 'Rapid relief of breakthrough cancer pain from 10 minutes', which although based on data from a study was inconsistent with the summary of product characteristics (SPC). The SPC stated that 'if adequate analgesia is not obtained within 15-30 minutes of administration of a single sublingual tablet, a second 100 microgram tablet may be administered'. The Panel had ruled a breach of the Code.

In Case AUTH/2235/5/09 the claims at issue were 'To hell and back in minutes' and that Abstral 'Acts in minutes'. The Panel considered that most readers would not consider 'in minutes' to be as long as 15 minutes. The Abstral SPC was specific with regard to times whereas the advertisement left it to the reader's judgement. The depiction of only three faces of a woman showing the transition from pain to relief, and the accompanying claim 'Dissolves in seconds' added to the impression that Abstral acted quickly. The Panel considered that by not giving more information as to the time Abstral took to act the claims 'Acts in minutes' and 'To hell and back in minutes' were misleading and inconsistent with the SPC. Breaches of the Code were ruled. The Panel was concerned that new material had been developed which might imply to some readers an even quicker time to action than the 10 minute claim previously ruled in breach.

The Panel considered that although there were some differences between the two cases, the claims at issue appeared to show a complete disregard for the previous ruling and were sufficiently similar to be covered by the undertaking previously given. High standards had not been maintained and the failure to comply with the undertaking reduced confidence in and brought discredit upon the pharmaceutical industry. Breaches of the Code were ruled including Clause 2. The Panel had also reported ProStrakan to the Appeal Board.

Turning to the case now at issue, Case AUTH/2268/9/09, the Panel noted that the advertisement in question in Case AUTH/2235/5/09 had been re-used in the BMJ on 12 September. The Panel ruled a breach of the Code. The Panel noted that ProStrakan's agent, had emailed a number of journals to inform them that the advertisement and related materials should not be used. It was not stated why the advertisement had been withdrawn and nor, with one exception for a journal in which advertising was pending, had ProStrakan or its agent requested written confirmation that the email had been received, the advertisement withdrawn and file copies destroyed. Thus the Panel did not consider that ProStrakan's procedures for withdrawing material were sufficiently robust and so in that regard high standards had not been maintained. A breach of the Code was ruled.

The Panel considered that ProStrakan had made some effort to comply with its undertaking and although its procedures should have been more robust, it had been badly let down by the BMJ. Asking all publishers for confirmation that emails had been received and that material had been destroyed/deleted might have avoided the

problem. Informing publishers why material was being withdrawn would emphasise the need to comply with the withdrawal notice. On balance, however the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code.

Cephalon (UK) Limited complained about an Abstral (sublingual fentanyl citrate) advertisement (ref MO17/0134) issued by ProStrakan which appeared in the BMJ 12 September.

As the complaint alleged a breach of the undertakings given in Cases AUTH/2207/2/09 and AUTH/2235/5/09 it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

COMPLAINT

Cephalon stated that it had a serious concern relating to Case AUTH/2235/5/09, in which materials were ruled to be in breach of the undertaking given in Case AUTH/2207/2/09. In Case AUTH/2235/5/09 the Panel ruled a breach of Clause 2 and had reported ProStrakan to the Code of Practice Appeal Board.

Cephalon alleged that unfortunately, the advertisement that had been part of the re-issued campaign in Case AUTH/2235/5/09 was published in the BMJ on 12 September 2009. This appeared to be not only a breach of the undertaking given in Case AUTH/2207/2/09, but also in breach of that given in Case AUTH/2235/5/09. Cephalon alleged breaches of Clause 25 of the Code.

Cephalon was told about the ruling in Case AUTH/2235/5/09 on 23 June 2009. It appeared that ProStrakan had failed to ensure that all materials were withdrawn as required by the undertaking. Sufficient time had elapsed to allow ProStrakan to halt any printing of previously purchased advertising space in the BMJ.

* * * * *

ProStrakan was asked to comment in relation to Clauses 2 and 9.1 of the Code in addition to Clause 25 as cited by Cephalon.

* * * * *

RESPONSE

ProStrakan understood the significance of an undertaking and was extremely concerned by the publication of the advertisement. ProStrakan explained that it used an agency to buy its advertising space, an advertising agency to manage the placement of the original advertisement and a different advertising agency for the management of a new advertisement.

The events following Case AUTH/2235/5/09 were as follows:

- 23 June 2009. The Authority notified ProStrakan of the outcome of Case AUTH/2235/5/09

- 24 June. ProStrakan telephoned the advertising agency to discuss the ruling and clarify the need for immediate withdrawal of the advertisement in question. At a meeting with the buying agency ProStrakan made it clear that all advertising in all journals for July and August was to be cancelled.

- 25 June. ProStrakan emailed the buying agency to confirm that the only pending advertisement, in the August edition of Pain, should be cancelled. The publishers of Pain confirmed that the Abstral materials had been deleted.

- 26 June. The advertising agency emailed all affected journals, informing them that the advertisement and related materials should not be used and must be deleted from systems and that new copy would be supplied in due course. The message was sent to the BMJ.

- 30 July. The new advertising agency sent new artwork to the BMJ for the September issue.

- 16 September. ProStrakan discovered the withdrawn advertisement in the 12 September edition of the BMJ and immediately contacted the PMCPA to report the discovery. ProStrakan initiated an investigation via its buying agency, which contacted the BMJ. The BMJ wrote to ProStrakan's buying agency acknowledging that the advertisement was out of date and had been replaced by new copy sent on 30 July 2009 by the new advertising agency. The BMJ also stated that the use of the incorrect advertisement was due to an issue at the BMJ.

  ProStrakan also contacted all UK and international journals, via its agents, to ensure that all journals had received and understood the withdrawal notification and also that they had received the new artwork. All journals confirmed withdrawal had occurred and that new artwork was in place.

- 17 September. ProStrakan wrote to the BMJ to highlight the serious nature of the error and request details of the original withdrawal and receipt of new artwork.

- 18 September. Initial response from the BMJ was received.

- 25 September. The BMJ responded in full.

- 29 September. ProStrakan contacted the BMJ to request the results of the investigation into the error and seek assurances that appropriate remedial action had been taken.

- 30 September. The BMJ responded with details of its investigation and corrective actions taken.

ProStrakan submitted that it had taken three key

steps to ensure that the advertisement was not used again. Firstly, a clear withdrawal notification was promptly issued to all journals. Secondly, ProStrakan checked with its agents to identify any pending advertising that used the withdrawn material; this revealed that the August edition of Pain was the only journal affected. Notification of destruction was immediately sought and received from the publishers. Thirdly, new advertising copy was issued and sent to the BMJ and other journals.

ProStrakan submitted that the BMJ had admitted serious failings on its part, both in the withdrawal of the advertisement and the use of new copy. The BMJ accepted that the appropriate individual with relevant responsibility received a timely, clear message about withdrawal. This was the usual method for notification of withdrawal, used by other clients, and should not have required any further action on the part of ProStrakan. Similarly, the new advertising copy was sent to the appropriate individuals at the BMJ.

ProStrakan submitted that it acted immediately on discovering the advertisement and contacted the PMCPA to report the matter. The BMJ was contacted to initiate an investigation. ProStrakan's agents wrote to all UK and European journals that had received Abstral copy to confirm receipt of withdrawal notification, destruction of affected materials and receipt of new advertising copy. All journals stated that they had complied with the original instruction and were using new copy.

ProStrakan acknowledged that, under the Code, it was wholly responsible for the actions of its agents and third parties. ProStrakan accepted that the initial notification to the BMJ should have made it clear that the advertisement was being withdrawn due to a breach of the Code. This notification should have also included more detail about the affected advertisement, particularly the number of iterations and scheduled dates of use. Additionally, ProStrakan should have sought written confirmation from the BMJ that the advertisement had been withdrawn and any copies destroyed or deleted. ProStrakan noted that it was currently reviewing and updating its Code compliance procedures and would be audited by the PMCPA in January 2010. ProStrakan knew its procedures in this area needed to be strengthened and would ensure that lessons learned from this incident were incorporated into its processes.

ProStrakan submitted that the BMJ had established that the root cause of this issue was human error. ProStrakan did not anticipate that a high-profile journal such as the BMJ would fail to act on a clear withdrawal notice and then compound that error by failing to use new advertising material. ProStrakan had sought and received assurances from the BMJ that its processes had been changed to protect against a similar problem in future.

ProStrakan was extremely disappointed that this situation had arisen and it would take all measures necessary to ensure it did not recur.

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/2207/2/09 the claim at issue, 'Rapid relief of breakthrough cancer pain from 10 minutes', which although based on data from a study was inconsistent with the summary of product characteristics (SPC). The SPC stated that 'if adequate analgesia is not obtained within 15-30 minutes of administration of a single sublingual tablet, a second 100 microgram tablet may be administered'. The Panel had ruled a breach of Clause 3.2 of the Code.

In Case AUTH/2235/5/09 the claims at issue were 'To hell and back in minutes' and that Abstral 'Acts in minutes'. The Panel considered that most readers would not consider 'in minutes' to be as long as 15 minutes. The Abstral SPC was specific with regard to times whereas the advertisement left it to the reader's judgement. The depiction of only three faces of a woman showing the transition from pain to relief, and the accompanying claim 'Dissolves in seconds' added to the impression that Abstral acted quickly. The Panel considered that by not giving more information as to the time Abstral took to act the claims 'Acts in minutes' and 'To hell and back in minutes' were misleading and in breach of Clause 7.2. A breach of Clause 3.2 was also ruled due to the claims' inconsistency with the SPC. The Panel was concerned that new material had been developed which might imply to some readers an even quicker time to action than the 10 minute claim previously ruled in breach.

The Panel considered that although there were some differences between the two cases, the claims at issue appeared to show a complete disregard for the previous ruling and were sufficiently similar to be covered by the undertaking previously given. A breach of Clause 25 was ruled. High standards had not been maintained and the failure to comply with the undertaking reduced confidence in and brought discredit upon the pharmaceutical industry. Breaches of Clauses 9.1 and 2 were ruled. The Panel had also reported ProStrakan to the Appeal Board.

Turning to the case now at issue, Case AUTH/2268/9/09, the Panel noted that the advertisement in question in Case AUTH/2235/5/09 had been re-used in the BMJ on 12 September. The Panel ruled a breach of Clause 25 of the Code. The Panel noted that ProStrakan's advertising agency had emailed a number of journals to inform them that the advertisement and related materials should not be used. It was not stated why the advertisement had been withdrawn and nor, with one exception for a journal in which advertising was

pending, had ProStrakan or its agent requested written confirmation that the email had been received, the advertisement withdrawn and file copies destroyed. Thus the Panel did not consider that ProStrakan's procedures for withdrawing material were sufficiently robust and so in that regard high standards had not been maintained. A breach of Clause 9.1 of the Code was ruled.

The Panel considered that ProStrakan had made some effort to comply with its undertaking and although its procedures should have been more robust, it had been badly let down by the BMJ. Asking all publishers for confirmation that emails had been received and that material had been destroyed/deleted might have avoided the problem. Informing publishers why material was being withdrawn would emphasise the need to comply with the withdrawal notice. On balance, however the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code.

Complaint received **16 September 2009**

Case completed **30 October 2009**

CASE AUTH/2271/10/09

VOLUNTARY ADMISSION BY ROCHE

Failure to certify an advertisement

Roche voluntarily admitted that due to a misunderstanding of its certification procedure, an advertisement for Avastin (bevacizumab) was published in the BMJ before it had been fully certified.

The detailed response from Roche is given below.

The Authority's Constitution and Procedure provided that a voluntary admission should be treated as a complaint if it related to a serious breach of the Code. Failure to certify was a serious matter and the Director decided to take the matter up as a complaint.

The Panel noted that the advertisement had been published prior to certification. A breach of the Code was ruled as acknowledged by Roche. The Panel considered that the failure to certify prior to publication meant that high standards had not been maintained. A breach of the Code was ruled. The Panel noted that once it knew of the error Roche had taken action both with the individual concerned and more widely with the marketing teams as a whole, to ensure that journal advertisements were not published before final certification.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such use. No breach of that clause was ruled.

Roche Products Limited voluntarily admitted that a journal advertisement for Avastin (bevacizumab) (AVAB00055a) had not been certified before publication.

Paragraph 5.4 of the Authority's Constitution and Procedure provided that a voluntary admission should be treated as a complaint if it related to a serious breach of the Code. Failure to certify was a serious matter and the Director decided to take the matter up as a complaint.

COMPLAINT

Roche noted an error in final certification of a journal advertisement which had appeared in the BMJ throughout September. The advertisement was not finally certified prior to publication because a single employee misunderstood the process.

A line manager identified the error when she was asked to sign the job bag containing the published advertisement. The manager explained to the individual concerned that in the case of a journal advertisement a colour pdf of the proof sent to the printers, including cutter guide and exact dimensions, and not the actual final journal, should be finally certified. The journal itself should then be placed in the job bag once published.

The individual, who returned from a leave of absence earlier in 2009, had since received full ABPI standard operating procedure (SOP) training, thought that the final article itself, ie the journal, needed to be certified, as was the case with other promotional items. The identified training need had been addressed by means of the manager's explanation and the individual was now fully aware of the process. The advertisement had been finally certified, and the certification form and the file note added to the job bag.

Roche submitted that the matter was reported to the compliance team and to the head of medical affairs as soon as it was discovered. The company apologised for the error.

The Authority asked Roche to provide it with any further comments that the company might have in relation to Clauses 2, 9.1 and 14.1 of the Code.

RESPONSE

Roche repeated its explanation above and stated that it did not believe that the misunderstanding identified was widespread. Nonetheless a marketing manager presented the case at a recent marketing team meeting to highlight this issue. Additionally, the medical director had emailed all of the marketing teams detailing the correct process. There were plans to develop a journal advertising guideline in conjunction with Roche's advertising and media buying agencies and these along with the message from the medical director would further ensure that this would not occur again.

Roche accepted that there was a breach of Clause 14.1 and expressed its regret. Immediate action was taken, and subsequent insertions of the advertisement were certified ahead of use with no amendments required. The advertisement was therefore certifiable in the form in which it appeared, having been through several prior rounds of approval.

Roche took adherence to the Code and maintenance of high standards very seriously, however in this instance it did not consider that high standards had not been maintained, and thus submitted that a breach of Clause 9.1 should not be ruled. The advertisement in question complied with the Code as detailed above – the issue was a failure to finally

certify. The issue, once identified, was rectified immediately through certification, and was brought to the Authority's attention in a timely manner.

Although Roche appreciated the critical importance of finally certifying items as detailed under Clause 14.1, it strongly believed that this particular case did not deserve the particular censure of a breach of Clause 2. Failure to certify, in this case, neither discredited nor reduced confidence in the pharmaceutical industry. As detailed above, following a rigorous review process prior to final certification, the advertisement was appropriate and complied with the Code. As soon as the issue was identified the advertisement was certified and no amendments were made.

PANEL RULING

The Panel noted that the advertisement had been published prior to certification. A breach of Clause 14.1 was ruled as acknowledged by Roche. The Panel considered that the failure to certify prior to publication meant that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel noted that once it knew of the error Roche had taken action both with the individual concerned and more widely with the marketing teams as a whole, to ensure that journal advertisements were not published before final certification.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such use. No breach of that clause was ruled.

Complaint received	**2 October 2009**
Case completed	**4 November 2009**

CODE OF PRACTICE REVIEW – NOVEMBER 2009

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

2231/5/09	**Bayer v Boehringer Ingelheim**	**Promotion of Pradaxa**	**Three Breaches Clauses 3.2 Breach Clause 4.1 Two Breaches Clause 7.2 Breaches Clauses 8.1 and 9.1**	**No appeal**	**Page 3**
2241/6/09	Consultants in Child and Adolescent Psychiatry v Lilly	Straterra support service	No breach	No appeal	Page15
2244/6/09	**General Practitioner and Pharmacist v Stiefel**	**Promotion of Duac**	**Breach Clause 3.2 Three breaches Clause 7.2 Breaches Clauses 7.4, 7.10, 9.1, 9.10 and 12.1**	**Appeal by complainants**	**Page 19**
2245/6/09	**Primary Care Trust Prescribing Support Unit v Lundbeck**	**Cipralex letter**	**Breaches Clauses 7.2, 7.4 and 9.1**	**No appeal**	**Page 32**
2246/7/09	**Roche/Director v Novartis**	**Zometa leavepiece**	**Breach Clause 3.2 Three Breaches Clause 7.2 Breach Clause 7.3 Three Breaches Clause 7.4 Breach Clause 7.5 Five Breaches Clause 7.8 Two Breaches 7.10 Breach Clause 8.1 Two Breaches Clause 9.1 Breach Clause 25**	**Appeal by respondent**	**Page 34**
2248/7/09	Member of the Public v Astellas Pharma	Conduct of representatives	No breach	No appeal	Page 59
2249/7/09	**Consultant Urological Surgeon v GlaxoSmithKline**	**Conduct of representatives**	**Breaches Clauses 7.2 and 15.2**	**No appeal**	**Page 62**
2250/7/09	**Voluntary admission By GlaxoSmithKline**	**Travel health proposal to a local buying group**	**Breaches Clauses 4.1, 4.3, 4.10, 7.2, 7.10, 9.1, 14.1, 15.2, and 18.4**	**No appeal**	**Page 66**
2251/7/09	Health Professional v Cephalon	Promotion of Effentora	No Breach	No appeal	Page 70
2252/7/09	**Professor v CV Therapeutics**	**Conduct of representative**	**Breach Clause 15.3**	**Appeal by complainant**	**Page 73**
2253/7/09	**Consultant Psychiatrist v Janssen-Cilag**	**Promotion of Risperdal Consta**	**Breaches Clauses 7.2, 7.4,15.2 and 15.9**	**No appeal**	**Page 81**
2255/8/09	**General Practitioner and Pharmacist v Stiefel**	**Sponsored journal insert**	**Breach Clause 2**	**No appeal**	**Page 85**

2256/8/09	**Health and Social Care Board Prescribing adviser v Napp**	**Promotion of Targinact**	**Two breaches Clause 7.2 Two breaches Clause 7.3 Breach Clause 9.1**	**No appeal**	**Page 87**
2257/8/09	**Voluntary admission by Ferring**	**Information sent to patient group**	**Breaches Clauses 2, 9.1, 14.3, 22.2 and 23.6**	**No appeal**	**Page 94**
2260/9/09	**Voluntary admission by Boehringer Ingelheim**	**Conduct of representative**	**Breaches Clauses 7.2, 7.4, 7.9, 8.1, 9.1 and 15.2**	**No appeal**	**Page 100**
2261/9/09	**Voluntary admission by Merck Sharp & Dohme**	**Breach of undertaking**	**Breach Clause 25**	**No appeal**	**Page 103**
2263/9/09	**Bristol-Myers Squibb v Boehringer Ingelheim**	**Viramune journal advertisement**	**Breach Clause 3.2**	**No appeal**	**Page 106**
2264/9/09	**Anonymous v GlaxoSmithKline**	**Invitation to a Satellite Symposium**	**Breach Clause 4.1**	**No appeal**	**Page 110**
2268/9/09	**Cephalon/Director v ProStrakan**	**Promotion of Abstral**	**Breaches Clauses 9.1 and 25**	**No appeal**	**Page 113**
2271/10/09	**Voluntary admission by Roche**	**Failure to certify an advertisement**	**Breaches Clause 9.1 and 14.1**	**No appeal**	**Page 117**

PMCPA | 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, over 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
- 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.

It also covers:

- the provision of information to the public either directly or indirectly, including by means of the Internet
- relationships with patient organisations
- the use of consultants
- non-interventional studies of marketed medicines
- grants and donations to institutions.

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 7747 8880
facsimile 020 7747 8881
by email to: complaints@pmcpa.org.uk.