NUMBER 74 November 2011

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.

RESPONDING TO A COMPLAINT

Every effort is made to ensure that complaints are dealt with as quickly and efficiently as possible. The Authority would be greatly helped in this regard if respondent companies ensured that all the necessary and relevant information was included in their response.

When submitting a response, you should ensure that all the documents requested by the case preparation manager have been provided. This is almost certain to include copies of all references cited in support of any claims in the materials at issue together with any other references cited in your response.

Consider asking someone who is not familiar with the matters at issue to read your submission to ensure that it sets out a comprehensive and well reasoned argument in response to the complaint and provides all of the necessary supporting documentation. As a respondent, you should try to put yourself in the Panel's position and consider what questions it would want answered and what documents it would want to see with regard to resolving the complaint at issue. Please ensure that you address each clause raised by the complainant or case preparation manager.

Requests for further information generally have to be met within five working days but wherever possible the information should be faxed or emailed to the Authority as soon as possible. If it is not clear to a company what information is required, it should make every effort to contact the member of the Authority who made the request.

ADVERSE EVENT REPORTING

Clause 4.10 states that all promotional material must include the prominent statement 'Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to [pharmaceutical company].'

Changes to the MHRA website mean that information on the yellow card scheme is now at yellowcard.mhra.gov.uk. Although the old web address (www.yellowcard.gov.uk) links straight to that site the Authority does not consider it unacceptable for companies to include the new web address (yellowcard.mhra.gov.uk) on their promotional material ahead of it being incorporated into the Code.

PMCPA WEBSITE

The PMCPA website is being redeveloped.

A survey conducted earlier this year with registered users of the site helped to identify areas for improvement. Thank you to all those who responded. A priority for the Authority is to improve the search function on the site and increase accessibility of the Code.

The new site will be launched in Summer 2012. For more information please contact Vicky Edgecombe on 020 7747 8884 or email vedgecombe@pmcpa.org.uk.

ENGAGING WITH THE PMCPA

The Authority is keen to enhance its communication with pharmaceutical companies, communications and advertising agencies, patient organisations and others who work with the Code. One of the Authority's roles is to provide informal advice and guidance about the Code and with this in mind we are trialling different ways of working with those who use the Code.

PMCPA Discussion Forum

In September we held the first PMCPA Discussion Forum which provided an opportunity for those in pharmaceutical companies who work with and interpret the Code to discuss topics of interest or areas of concern with the PMCPA. Attendees at the first meeting were from a variety of roles including communications, marketing, medical, medical information and compliance. Topics discussed included digital communications, changes to the Code, EFPIA and IFPMA codes, and an open question and answer session. The second meeting will take place in Spring 2012.

PMCPA Compliance Network

The PMCPA Compliance Network met for the first time in November. The agenda included a review of recent cases and queries, changes to the Code, discussion of changing regulations in Europe and UK, and an update on the redevelopment of the PMCPA website. The second meeting of the Compliance Network will take place on 25 January 2012.

For further information about these groups please contact Vicky Edgecombe on 020 7747 8884 or email vedgecombe@pmcpa.org.uk.

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:
Friday, 3 February 2012

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
7th Floor, Southside, 105 Victoria Street, London SW1E 6QT

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
Ros Henley	020 7747 8883

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/2403/5/11

GENERAL PRACTITIONER v BOEHRINGER INGELHEIM

Press article about Pradaxa

A general practitioner complained about an article about Pradaxa (dabigatran) which appeared in the Daily Mail on 5 April 2011. The on-line version of the article featured a colour photograph of the lower half of the face of an apparently young woman about to put a tablet into her mouth. Pradaxa, produced by Boehringer Ingelheim, was indicated for the prevention of venous thromboembolic events in adults who had undergone elective total hip or knee replacement surgery.

The complainant's primary concern was that the article disparaged warfarin which was described as rat poison. Immediately below the image Pradaxa was described as a 'wonder drug', but it had yet to be launched in the UK.

The complainant considered that the article promoted a prescription only medicine to the public. The information supplied was not balanced as it disparaged the use of warfarin and made excessive claims about the benefits, safety and effectiveness of Pradaxa in comparison. The complainant questioned the suitability and taste of the article. The featured image was of a sexual nature and appeared to attract the reader's attention. A woman of her apparent age was unlikely to be that of the expected recipient.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that the Code prohibited the advertising of prescription only medicines to the public. Information about prescription only medicines could be supplied directly or indirectly to the public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific prescription only medicine. Complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself. It appeared that the complainant had not seen Boehringer Ingelheim's press materials. The complaint was based on the press article.

The Panel noted that the press release, entitled 'Dabigatran etexilate provides consistent benefit irrespective of patient's atrial fibrillation type' discussed the comparative data in relation to stroke prevention derived from various analyses of the Randomized Evaluation of Long-Term Anti-coagulant Therapy (RE-LY) study (Connelly *et al* 2009, Connelly *et al* 2010a and Flaker *et al* 2011). The Panel was also given a copy of Connelly *et al* (2010b), a supplementary appendix provided by Boehringer Ingelheim, which had been provided by the authors to give readers additional information.

The Panel noted that the press release mentioned warfarin solely in relation to its use as a comparator in Flaker *et al* and the Connolly *et al* studies. It did not refer to warfarin as rat poison and otherwise made no disparaging remarks about the medicine. The Panel had no evidence about how warfarin had been described by Boehringer Ingelheim's spokespersons or at any press conference. No breach of the Code was ruled in that regard.

The Panel considered that it had to decide whether the press release provided sufficient detail to constitute factual and balanced information about Pradaxa with regard to the overall outcome of the RE-LY study. The Panel noted that compared with warfarin, dabigatran 150mg was associated with lower rates of stroke and systemic embolism, but similar rates of major haemorrhage and a significantly higher rate of major gastrointestinal bleeds. However, the net clinical benefit outcome rate showed an advantage for dabigatran 150mg compared with well-controlled warfarin. The Panel noted that the summary of product characteristics (SPC) for warfarin included 'risk of haemorrhage' in section 4.4 'Special warnings and precautions for use'.

The press release stated that, compared to well-controlled warfarin, 150mg dabigatran twice daily showed a 39% reduction in the risk of stroke in patients with paroxysmal atrial fibrillation, 36% reduction in the risk of stroke in patients with persistent atrial fibrillation and a 30% reduction in the risk of stroke in patients with permanent atrial fibrillation. The press release also stated that dabigatran 110mg twice daily compared with well-controlled warfarin demonstrated similar efficacy in patients with paroxysmal, persistent and permanent atrial fibrillation. There was no mention of major haemorrhage in the press release.

The Panel considered that omitting from the press release data in relation to the bleeding risk associated with dabigatran in comparison with warfarin meant that the press release was not balanced. A breach of the Code was ruled.

The Panel noted that the press release did not refer to dabigatran as a 'wonder drug' as the Daily Mail article had. The Panel had no evidence about how

dabigatran had been described by Boehringer Ingelheim's spokespersons or at any press conference. The Panel was concerned about the very positive statements in the 'Notes to Editors' section of the press release which described Pradaxa as 'leading the way in new oral anticoagulants/direct thrombin inhibitors …targeting a high unmet medical need' and queried whether this was a fair reflection of the evidence. However, in this instance, the Panel did not consider that the press release constituted an advertisement to the public for a prescription only medicine, and ruled no breach of the Code in that regard.

The Panel noted that Boehringer Ingelheim had not provided the image to the Daily Mail and neither did its media agency, and ruled no breach of the Code in that regard.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure, and was reserved for such circumstances. The Panel did not consider that the press release brought discredit upon or reduced confidence in the industry, and ruled no breach of Clause 2.

A general practitioner complained about an article about Pradaxa (dabigatran) which appeared in the Daily Mail on 5 April 2011. His attention had been drawn to the article by a health news story that appeared on the NHS Choices website. The on-line version of the Daily Mail article featured a colour photograph of the lower half of the face of an apparently young woman about to put a tablet into her mouth. Pradaxa, produced by Boehringer Ingelheim Limited, was indicated for the prevention of venous thromboembolic events in adults who had undergone elective total hip or knee replacement surgery.

COMPLAINT

The complainant stated that his primary concern was that the article in the Daily Mail breached Clause 8.1 in that it disparaged the comparator medicine ('Warfarin, routinely used as rat poison, has been prescribed to prevent strokes since the 1950s'). Immediately below the image Pradaxa was described as a 'wonder drug', but it had yet to be launched in the UK.

The complainant wondered if the article breached Clause 22.2 in that it appeared to promote a prescription only medicine directly to the public. If so, then the information supplied was not balanced as it had disparaged the use of warfarin and made excessive claims about the benefits, safety and effectiveness of Pradaxa in comparison.

The article breached the Code with regard to suitability and taste (Clauses 9.1 and 9.2). The featured image was of a sexual nature and appeared to attract the attention of the reader to the article. A woman of her apparent age was unlikely to be that of the expected recipient.

In addition to the clauses cited by the complainant Boehringer Ingelheim was asked by the Authority to respond in relation to Clauses 2 and 22.1 of the Code.

RESPONSE

Boehringer Ingelheim explained that the Daily Mail article was published as the 60th Session of the American College of Cardiology (ACC) Conference 2011 took place in New Orleans. At the ACC Conference new data was presented on the use of dabigatran in atrial fibrillation (AF) patients. In conjunction with the ACC Conference a certified press release was released to the media on Tuesday, 5 April 2011. This press release was newsworthy, factually correct and a fair and balanced presentation of the new data presented at the conference.

Boehringer Ingelheim firmly asserted that this press release was entirely appropriate and complied with Clause 22.2 of the Code – it was factual, fair and balanced, did not raise unfounded hopes of successful treatment and was not made specifically to encourage members of the public to ask their health professional to prescribe a prescription only medicine.

Boehringer Ingelheim explained that the Daily Mail journalist telephoned Boehringer Ingelheim's PR agency to express an interest in dabigatran and request a copy of the press release. On speaking with the journalist, the press release embargo was highlighted and she was directed to various spokespeople available. As a follow up to the telephone call, the PR agency emailed the journalist a copy of the certified press release; no other material was sent. Copies of the covering email and the press release were provided.

Boehringer Ingelheim noted that the press release did not contain any disparaging remarks about warfarin. As stated above, the press release was factual, fair and balanced. Nor was there any reference to 'wonder drug' in the press release. The company therefore strongly refuted the alleged breach of Clause 8.1.

As stated above, the Code allowed information on medicines in development to be provided to the public as long as it was factual, fair and balanced. Equally Boehringer Ingelheim firmly believed that the press release would not encourage members of the public to ask their health professional to prescribe a prescription only medicine. The press release did not promote Pradaxa to the public. Boehringer Ingelheim therefore strongly refuted the alleged breach of Clause 22.2.

The image used by the Daily Mail on-line was not provided by Boehringer Ingelheim or its media agency and so there was no breach of Clauses 9.1 and 9.2 of the Code.

Boehringer Ingelheim believed that it had

demonstrated that its activities had been appropriate within the scope of the Code and it thus strongly refuted the allegations of breaches of the Code.

PANEL RULING

The Panel noted that Clause 22.1 prohibited the advertising of prescription only medicines to the general public. Clause 22.2 permitted information about prescription only medicines to be supplied directly or indirectly to the public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific prescription only medicine. Complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself. It appeared that the complainant had not seen Boehringer Ingelheim's press materials. The complaint was based on the press article.

The Panel noted that the press release, entitled 'Dabigatran etexilate provides consistent benefit irrespective of patient's atrial fibrillation type' discussed the comparative data in relation to stroke prevention from Flaker *et al* (2011) a sub-group analysis of the Randomized Evaluation of Long-Term Anti-coagulant Therapy (RE-LY) study, Connelly *et al* (2009) the RE-LY study and Connelly *et al* (2010a) newly identified events in the RE-LY study.

Connolly *et al* (2009) was a randomized, non-inferiority trial that assigned atrial fibrillation patients who had a risk of stroke to receive, in a blinded fashion, a fixed dose of dabigatran (110mg or 150mg twice daily) or, in an unblinded fashion, warfarin. The primary outcome was stroke or systemic embolism. The statistical analysis section stated that the primary analysis was to test whether either dose of dabigatran was non-inferior to warfarin and that after non-inferiority of both doses of dabigatran was established, all subsequent p values were reported for two-tailed tests of superiority. It was unclear whether some differences which were described as superior achieved statistical significance. Connelly *et al* (2009) concluded that in relation to the primary outcome, both doses of dabigatran were non-inferior to warfarin ($p<0.001$). The 150mg dose was also superior to warfarin ($p<0.001$), but the 110mg dose was not ($p=0.34$). The Connelly *et al* (2010b) supplementary appendix provided by Boehringer Ingelheim, which had been provided by the authors to give readers additional information about their work, indicated that the 110mg dabigatran dose was not superior to warfarin for the primary outcome, stroke or systemic embolism, $p=0.29$. Dabigatran 150mg and warfarin produced similar rates of any major bleeding ($p=0.31$), whereas the 110mg dabigatran dose had a lower rate of major bleeding compared with warfarin ($p=0.003$). These p values were the same in Connelly *et al* (2010a). Connelly *et al* (2009 and 2010b) showed that there was a significantly higher rate of major gastrointestinal bleeding with dabigatran 150mg than with warfarin ($p<0.001$ and $p=0.001$, respectively).

However, Connelly *et al* (2009) noted that the rates of 'combined net clinical benefit outcome', (which was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, major bleeding and death and was thus a measure of the overall benefit and risk) were 7.64% per year for warfarin, 7.09% per year for dabigatran 110mg ($p=0.10$) and 6.91% per year for dabigatran 150mg ($p=0.04$). The net clinical benefit was almost identical for both doses. Subsequent re-analysis published in Connolly *et al* (2010b) noted that the net clinical benefit outcome rates were 7.91% per year for warfarin, 7.34% per year for dabigatran 110mg and 7.11% per year for dabigatran 150mg. The p value for the difference between dabigatran 110mg vs warfarin was $p=0.09$ and for dabigatran 150mg vs warfarin $p=0.02$. Connelly *et al* (2009) concluded that the net clinical benefit was similar between the two doses of dabigatran, due to the lower risk of ischemia with the 150mg dose and the lower risk of haemorrhage with the 110mg dose.

Flaker *et al* also noted that dabigatran 150mg twice daily was more effective than warfarin in stroke prevention across all atrial fibrillation types, and noted a similar rate with that dose to warfarin for major bleeding events. In this analysis, the Panel noted that p values were provided for major bleeding episodes in persistent atrial fibrillation, $p=0.58$, a result described as non significant and the phrase 'The p-value for interaction was 0.16' appeared after a sentence which described the differences between warfarin and dabigatran 110mg (similar efficacy) and 150mg (more effective) across atrial fibrillation types.

The press release stated that, compared to well-controlled warfarin, 150mg dabigatran twice daily showed a 39% reduction in the risk of stroke in patients with paroxysmal atrial fibrillation, 36% reduction in the risk of stroke in patients with persistent atrial fibrillation and a 30% reduction in the risk of stroke in patients with permanent atrial fibrillation. The press release also stated that dabigatran 110mg twice daily compared with well controlled warfarin demonstrated similar efficacy in patients with paroxysmal, persistent and permanent atrial fibrillation. There was no mention of major haemorrhage in the press release.

The Panel noted that the press release mentioned warfarin solely in relation to its use as a comparator in Flaker *et al* and the Connolly *et al* studies. It did not refer to warfarin as rat poison and otherwise made no disparaging remarks about the medicine. The Panel had no evidence about how warfarin had been described by Boehringer Ingelheim's spokespersons or at any press conference. No breach of Clause 8.1 was ruled in that regard.

In relation to the requirements of Clause 22.2, the Panel considered that it had to decide whether the press release provided sufficient detail to constitute factual and balanced information about Pradaxa with regard to the overall outcome of the RE-LY study. The Panel noted that compared with warfarin, dabigatran 150mg was associated with lower rates of stroke and systemic embolism, but similar rates of major haemorrhage and a significantly higher rate of major gastrointestinal bleeds. However, the net clinical benefit outcome rate showed an advantage for dabigatran 150mg compared with well-controlled warfarin. The Panel noted that the summary of product characteristics (SPC) for warfarin included 'risk of haemorrhage' in section 4.4 'Special warnings and precautions for use'.

The Panel considered that omitting from the press release data in relation to the bleeding risk associated with dabigatran in comparison with warfarin meant that the press release was not balanced in the way that it presented the medicine. A breach of Clause 22.2 was ruled.

The Panel noted that Boehringer Ingelheim was asked to respond in relation to Clause 22.1 of the Code, but had not done so. The Panel noted that the press release did not refer to dabigatran as a 'wonder drug' as the Daily Mail article had. The Panel had no evidence about how dabigatran had been described by Boehringer Ingelheim's spokespersons or at any press conference. The Panel was concerned about the very positive statements in the 'Notes to Editors' section of the press release which described Pradaxa as 'leading the way in new oral anticoagulants/direct thrombin inhibitors …targeting a high unmet medical need' and queried whether this was a fair reflection of the evidence. However, in this instance, the Panel did not consider that the press release constituted an advertisement to the public for a prescription only medicine, and ruled no breach of Clause 22.1 in that regard.

In relation to the alleged breach of Clause 9.1 and 9.2 with regard to the suitability of the image in the Daily Mail article, the Panel noted Boehringer Ingelheim's submission that it did not provide the image to the Daily Mail and neither did its media agency, and ruled no breach of Clauses 9.1 and 9.2 in that regard.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure, and was reserved for such circumstances. The Panel did not consider that the press release brought discredit upon or reduced confidence in the industry, and ruled no breach of Clause 2.

Complaint received	**5 May 2011**
Case completed	**20 July 2011**

CASE AUTH/2404/5/11

GENERAL PRACTITIONER v BOEHRINGER INGELHEIM

Promotion of Pradaxa

A general practitioner complained that a number of articles about Boehringer Ingelheim's product Pradaxa (dabigatran) which appeared in the Daily Mail, The Telegraph and the Express on 5 April 2011, referred to the use of the medicine to prevent stroke, an unlicensed indication.

Pradaxa was indicated for the primary prevention of venous thromboembolic events in adults who had undergone elective total hip or knee replacement surgery. Boehringer Ingelheim had made an application to the European Medicines Agency (EMA) to extend the licence to prevention of stroke and systemic embolism in atrial fibrillation.

The complainant was concerned that the articles contained exaggerated claims about Pradaxa which had arisen from misleading press releases issued by Boehringer Ingelheim. The coverage contained quotations from UK experts and patient group representatives and it was likely that Boehringer Ingelheim had facilitated access to these individuals and approved this unlicensed promotion of Pradaxa within the UK.

The claims for stroke prevention were based on a retrospective subanalysis of the Randomized Evaluation of Long-Term Anti-coagulant Therapy (RE-LY) study (Connolly *et al* 2009), which compared the effect of Pradaxa with warfarin in preventing strokes in people with atrial fibrillation. The complainant noted that this promotion took place after an application was made to the EMA to extend the licence of Pradaxa for the prevention of thromboembolism and stroke in people with atrial fibrillation and the recent approval by the Food and Drug Administration (FDA) for the same.

The complainant also alleged that the press articles disparaged warfarin, a current option, referring to it as a rat poison. The complainant noted that packs of Pradaxa were also pictured.

The complainant alleged that the promotion to the public of an unlicensed indication was irresponsible and would encourage the public to seek the prescription of Pradaxa for this purpose.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that the Code prohibited the advertising of prescription only medicines to the public. However, the Code permitted information about prescription only medicines to be supplied directly or indirectly to the public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine. Complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself.

The Panel noted that Boehringer Ingelheim had engaged as spokespeople two health professionals and two patient organisation representatives. At least one of the health professionals was briefed by Boehringer Ingelheim's media agency, and the company had facilitated the availability of the spokespersons for interviews. The Panel considered that Boehringer Ingelheim was responsible under the Code for comments made by these spokespersons. Companies could not use independent experts as a means of avoiding the restrictions in the Code. The Panel noted that the contract between Boehringer Ingelheim and one health professional spokesperson referred to some of the requirements of the Code, but did not refer either to the prohibition on the promotion of prescription only medicines to the public or the Code requirements on the content of information directed at the public. The Panel considered that this was a significant omission particularly as the press release was aimed at the consumer press.

The Panel noted that the health professional spokesperson briefed by Boehringer Ingelheim's media agency was quoted in the press release issued by Boehringer Ingelheim to the consumer press and that some of the press articles included further quotes from him and other spokespersons. The Panel was concerned that this health professional spokesperson was quoted in The Telegraph article describing Pradaxa as preventing 'clots better than warfarin but with less bleeding which is pretty much the holy grail for such drugs'.

The Panel noted that the press release discussed the comparative data in relation to stroke prevention from Flaker *et al* (2011) a sub-group analysis of the RE-LY study, Connelly *et al* (2009) the RE-LY study and Connelly *et al* (2010a) newly identified events in the RE-LY

study. The press release included quotations from the same health professional which described Pradaxa as an 'invaluable option' for patients. The press release did not include the pack shot.

The press release stated that, compared to well-controlled warfarin, 150mg dabigatran twice daily showed a 39% reduction in the risk of stroke in patients with paroxysmal atrial fibrillation, 36% reduction in the risk of stroke in patients with persistent atrial fibrillation and a 30% reduction in the risk of stroke in patients with permanent atrial fibrillation. There was no mention of major haemorrhage or any other adverse event in the press release. The Panel noted that Pradaxa was not authorized for use in atrial fibrillation. The Panel questioned whether in the absence of information in the consumer press release about side effects the press release was balanced.

The Panel noted that the press release mentioned warfarin solely in relation to its use as a comparator in Flaker *et al* and the RE-LY studies. It did not refer to warfarin as rat poison and otherwise made no disparaging remarks about the medicine. The Panel had no evidence about how warfarin had been described by Boehringer Ingelheim's spokespersons or at any press conference. No breach of the Code was ruled in that regard.

The Panel was concerned about the very positive statements in the 'Notes to Editors' section of the press release which described Pradaxa as 'leading the way in new oral anticoagulants/direct thrombin inhibitors ...targeting a high unmet medical need' and queried whether this was a fair reflection of the evidence. The press release did not refer to Pradaxa as a 'super pill' or as a 'revolutionary drug'. These phrases only appeared in the press articles.

Overall the Panel was very concerned about the content of the press release and the briefing material for spokespersons. The Panel considered that these would in effect encourage members of the public to ask their health professional to prescribe a specific prescription only medicine. The Panel was concerned about the lack of information in a consumer press release relating to side effects. A breach of the Code was ruled. The press release advertised a prescription only medicine to the public for an unlicensed indication. The Panel ruled a breach of the Code in that regard. The Panel considered that promotion of Pradaxa for an unlicensed indication was inconsistent with the terms of its marketing authorization. A further breach of the Code was ruled.

The Panel considered that high standards had not been maintained and ruled a breach of the Code. The material promoted a prescription only medicine to the public in an indication that was not yet licensed. The Panel noted that promotion prior to the grant of a marketing authorization was listed as an example of an activity that was likely to be in breach of Clause 2. Overall the Panel considered that the press release and the material for spokespersons brought discredit upon, and reduced confidence in, the industry. A breach of Clause 2 was ruled.

A general practitioner complained that a number of articles about Pradaxa (dabigatran) which appeared in the Daily Mail, The Telegraph and the Express on 5 April 2011, referred to the use of the medicine to prevent stroke.

Pradaxa, produced by Boehringer Ingelheim Limited was indicated for the primary prevention of venous thromboembolic events in adults who had undergone elective total hip or knee replacement surgery. Boehringer Ingelheim had made an application to the EMA to extend the licence to prevention of stroke and systemic embolism in atrial fibrillation.

COMPLAINT

The complainant was concerned that an article in the Daily Mail contained exaggerated claims about Pradaxa such as 'Super pill cuts risk of stroke for one million Britons' and that other UK newspapers described it as a 'revolutionary drug'. The complainant considered that these claims had arisen from misleading press releases issued by Boehringer Ingelheim and its nominated speakers. Given the extensive and exclusive use of quotations from UK experts and patient group representatives in the promotion of this unlicensed indication and its subsequent coverage in major newspapers it was likely that Boehringer Ingelheim had facilitated access to these individuals and approved this unlicensed promotion of Pradaxa within the UK.

The claims for the unlicensed indication, stroke prevention, were based on a retrospective subanalysis of the Randomized Evaluation of Long-Term Anti-coagulant Therapy (RE-LY) study (Connolly *et al* 2009). This retrospective analysis compared the effect of Pradaxa with warfarin in preventing strokes in people with atrial fibrillation and investigated whether the reduction in stroke risk with Pradaxa compared with warfarin was affected by how 'at risk' the person was for stroke and the type of atrial fibrillation they had.

The complainant noted that the promotion of the unlicensed indication took place after an application was made to the EMA to extend the licence of Pradaxa for the prevention of thromboembolism (blood clots) and stroke in people with atrial fibrillation and the recent approval by the FDA for the same.

The complainant noted that the press articles focused on the number of people who could be

treated with Pradaxa. The complainant stated that the reports accurately noted the benefits compared with warfarin in so much that Pradaxa did not need monitoring and dose adjustments but then unbalanced this discussion by referring to warfarin, a current option, as a rat poison, which was disparaging. The coverage also reported that Pradaxa treatment would be available within weeks, was unaffected by diet and would cost £2.50 a day. The complainant noted that packs of Pradaxa were also pictured in some of the press coverage.

The complainant alleged that the promotion to the public of an unlicensed indication was not only irresponsible but would encourage the public to seek the prescription of Pradaxa for this purpose.

The complainant stated that importantly, the news stories were based on press information which did not report the confidence intervals from the research. As such, the press releases were misleading as it was not possible to state whether the overall difference between warfarin and Pradaxa in reducing risk of stroke reported in 2009 was maintained when each of the subgroups receiving Pradaxa was compared with warfarin.

When writing to Boehringer Ingelheim, the Authority asked it to respond in relation to Clauses 2, 3.2, 8.1, 9.1, 22.1 and 22.2 of the Code.

RESPONSE

Boehringer Ingelheim stated that the articles in the Daily Mail, The Telegraph and Daily Express arose from a single press release from Boehringer Ingelheim (ref DBG2372) which reported data from a subgroup analyses of the RE-LY study. The press release followed the American College of Cardiology Conference 2011 and represented the data presented at the conference accurately and without exaggeration. The confidence intervals were given in the press release. Boehringer Ingelheim noted that the complainant had observed that confidence intervals were necessary to interpret the data and appeared to have taken his reference from the article on the NHS Choices website. Boehringer Ingelheim agreed, which was why the press release at issue included confidence intervals. Boehringer Ingelheim emphasised that it was committed to ensuring that any information it issued complied with the Code.

Boehringer Ingelheim noted that the complainant stated that the Daily Mail article disparaged warfarin, describing it as 'rat poison'. Boehringer Ingelheim had not and would not disparage an important, widely used and clinically valuable medicine in this way.

Boehringer Ingelheim did not communicate to the Daily Mail about the availability of Pradaxa for stroke prevention in atrial fibrillation in the UK. The company also did not discuss the cost of such treatment with the newspaper. None of the company's interactions or press releases were promotional. Boehringer Ingelheim strongly refuted the complainant's allegation that it had promoted an unlicensed indication; the press release at issue clearly stated that Pradaxa was unlicensed for stroke prevention in atrial fibrillation.

The image that appeared in the online version of the Daily Mail article was not provided by Boehringer Ingelheim or its media agency. Boehringer Ingelheim stated that it never provided pack shots to the media.

With regard to the clauses of the Code it had been asked to consider, Boehringer Ingelheim strongly refuted that its conduct in relation to the recent press articles brought discredit to, or reduced confidence in, the industry. The company firmly asserted that it had behaved appropriately, and denied a breach of Clause 2.

Pradaxa did not have a marketing authorization for stroke prevention in atrial fibrillation, and this was made clear in the press release at issue which was factual and non-promotional. Boehringer Ingelheim therefore denied a breach of Clause 3.2.

Boehringer Ingelheim submitted that the press release contained no disparaging remarks about warfarin. The press release was factual, fair and balanced. Boehringer Ingelheim therefore believed there was no breach of Clause 8.1.

Boehringer Ingelheim submitted that the Code allowed the provision to the public of information on medicines in development, as long as it was provided in a factual, fair and balanced way. Equally, Boehringer Ingelheim firmly believed that the press release would not encourage members of the public to ask their health professional to prescribe a prescription only medicine. The press release did not promote Pradaxa to the general public. Boehringer Ingelheim therefore denied a breach of Clause 22.1.

The image used by the Daily Mail was not provided by Boehringer Ingelheim or its agent. Boehringer Ingelheim submitted that its conduct was appropriate and complied with the Code. The company believed that high standards had been maintained in the press release and denied a breach of Clauses 9.1 or 9.2.

Based on the results of the RE-LY study, Pradaxa received a positive opinion on 15 April, 2011 from the Committee for Medicinal Products for Human Use (CHMP) for stroke prevention in patients with atrial fibrillation. The CHMP had recommended approval of Pradaxa in EU member states for the prevention of stroke and systemic embolism in adults with nonvalvular atrial fibrillation with one or more of the following risk factors:
Previous stroke, transient ischemic attack, or systemic embolism

- Left ventricular ejection fraction < 40 %

- Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2
- Age ≥ 75 years
- Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension.

A health professional and a representative from a patient organisation, both of whom were quoted in the Daily Mail article, had been engaged as spokespeople for Boehringer Ingelheim. The health professional had been media trained by Boehringer Ingelheim's media agency. Copies of the contracts and the briefing document for media training for this health professional were provided.

The article in The Telegraph further cited this health professional, a representative from another patient organisation and a health professional from the United States (US). Boehringer Ingelheim stated that it had no relationship with the health professional from the US and had no communication with him prior to the article in The Telegraph. Boehringer Ingelheim presumed that The Telegraph contacted him independently. The patient organisation representative was not a Boehringer Ingelheim spokesperson. Boehringer Ingelheim worked with, and had provided sponsorship for, that organisation.

The article in the Daily Express cited the patient organisation representative and UK health professional cited in the Telegraph article. Neither Boehringer Ingelheim or its media agency had any contact with the journalist who wrote the article.

Boehringer Ingelheim stated that it had provided the Daily Mail and The Telegraph with the names of its allocated spokespeople. A copy of this e-mail was provided.

Boehringer Ingelheim confirmed that the Daily Mail journalist telephoned its media agency expressing interest in Pradaxa and requesting a copy of the press release. The press release embargo was highlighted and the journalist was directed to the various spokespeople available. The media agency followed up the telephone call with an email and press release. A copy of this e-mail was provided. No other material was provided to the Daily Mail. Nor did Boehringer Ingelheim pay any of the newspapers.

Boehringer Ingelheim believed that it had demonstrated that its activities had been entirely appropriate and within the scope of the Code; it therefore strongly refuted the allegations of breaches of the Code.

PANEL RULING

The Panel noted that Clause 22.1 prohibited the advertising of prescription only medicines to the public. Clause 22.2 permitted information about prescription only medicines to be supplied directly or indirectly to the public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine. Complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself. It appeared that the complainant had not seen Boehringer Ingelheim's press materials. The complaint was based on the press articles.

The Panel noted that Boehringer Ingelheim had engaged as spokespeople two health professionals and two patient organisation representatives. At least one of the health professionals was briefed by Boehringer Ingelheim's media agency, and the company had facilitated the availability of the spokespersons for interviews. The Panel considered that Boehringer Ingelheim was responsible under the Code for comments made by these spokespersons. Companies could not use independent experts as a means of avoiding the restrictions in the Code. The Panel had a copy of the contract between Boehringer Ingelheim and one of the health professional spokespersons which referred to the Code, and in particular the requirements of Clauses 3.1, 7.2 and 7.4. However, there was no reference to the requirements of Clauses 22.1 or 22.2. The Panel considered that this was a significant omission particularly as the press release was aimed at the consumer press. The Panel did not have details about the media training nor the date and content of the national press conference.

The Panel noted that the health professional spokesperson briefed by Boehringer Ingelheim's media agency was quoted in the press release, and that some of the press articles included further quotes from him and other spokespersons. The Panel noted that it did not know what was said at any press conference, or during conversations between the company's media agency, the spokespersons and the journalists, but was concerned that the health professional was quoted in The Telegraph article describing Pradaxa as preventing 'clots better than warfarin but with less bleeding which is pretty much the holy grail for such drugs'.

The Panel noted that the press release, entitled 'Dabigatran etexilate provides consistent benefit irrespective of patient's atrial fibrillation type' discussed the comparative data in relation to stroke prevention from Flaker *et al* (2011) a sub-group analysis of the RE-LY study, Connelly *et al* (2009) the RE-LY study and Connelly *et al* (2010a) newly identified events in the RE-LY study. The press release included quotations from the health professional noted above. One quotation described Pradaxa as an 'invaluable option' for patients. The Panel noted that whilst the press release was

aimed at the consumer press it did not have general details about how and to whom it was circulated. The press release did not include the pack shot. The Panel noted Boehringer Ingelheim's submission that it never provided pack shots to the media.

Connolly *et al* (2009) was a randomized, non-inferiority trial that assigned atrial fibrillation patients who had a risk of stroke to receive, in a blinded fashion, a fixed dose of dabigatran (110mg or 150mg twice daily) or, in an unblinded fashion, warfarin. The primary outcome was stroke or systemic embolism. The statistical analysis section stated that the primary analysis was to test whether either dose of dabigatran was non-inferior to warfarin and that after non-inferiority of both doses of dabigatran was established, all subsequent p values were reported for two-tailed tests of superiority. It was unclear whether some differences which were described as superior achieved statistical significance. Connelly *et al* (2009) concluded that in relation to the primary outcome, both doses of dabigatran were non-inferior to warfarin ($p<0.001$). The 150mg dose was also superior to warfarin ($p<0.001$), but the 110mg dose was not ($p=0.34$). The Connelly *et al* (2010b) supplementary appendix provided by Boehringer Ingelheim, which had been provided by the authors to give readers additional information about their work, indicated that the 110mg dabigatran dose was not superior to warfarin for the primary outcome, stroke or systemic embolism, $p=0.29$. Dabigatran 150mg and warfarin produced similar rates of any major bleeding ($p=0.31$), whereas the 110mg dabigatran dose had a lower rate of major bleeding compared with warfarin ($p=0.003$). These p values were the same in Connelly *et al* (2010a). Connelly *et al* (2009 and 2010b) showed that there was a significantly higher rate of major gastrointestinal bleeding with dabigatran 150mg than with warfarin ($p<0.001$ and $p=0.001$, respectively).

However, Connelly *et al* (2009) noted that the rates of 'combined net clinical benefit outcome', (which was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, major bleeding and death and was thus a measure of the overall benefit and risk) were 7.64% per year for warfarin, 7.09% per year for dabigatran 110mg ($p=0.10$) and 6.91% per year for dabigatran 150mg ($p=0.04$). The net clinical benefit was almost identical for both doses. Subsequent reanalysis published in Connolly *et al* (2010b) noted that the net clinical benefit outcome rates were 7.91% per year for warfarin, 7.34% per year for dabigatran 110mg and 7.11% per year for dabigatran 150mg. The p value for the difference between dabigatran 110mg vs warfarin was $p=0.09$ and for dabigatran 150mg vs warfarin $p=0.02$. Connelly *et al* (2009) concluded that the net clinical benefit was similar between the two doses of dabigatran, due to the lower risk of ischemia with the 150mg dose and the lower risk of haemorrhage with the 110mg dose.

Flaker *et al* also noted that dabigatran 150mg twice daily was more effective than warfarin in stroke prevention across all atrial fibrillation types, and noted a similar rate with that dose to warfarin for major bleeding events. In this analysis, the Panel noted that p values were provided for major bleeding episodes in persistent atrial fibrillation, $p=0.58$, a result described as non-significant and the phrase 'The p-value for interaction was 0.16' appeared after a sentence which described the differences between warfarin and dabigatran 110mg (similar efficacy) and 150mg (more effective) across atrial fibrillation types. Confidence intervals were given.

The press release stated that, compared to well-controlled warfarin, 150mg dabigatran twice daily showed a 39% reduction in the risk of stroke in patients with paroxysmal atrial fibrillation, 36% reduction in the risk of stroke in patients with persistent atrial fibrillation and a 30% reduction in the risk of stroke in patients with permanent atrial fibrillation. There was no mention of major haemorrhage or any other adverse event in the press release. The Panel noted that Pradaxa was not authorized for use in atrial fibrillation. The Pradaxa summary of product characteristics (SPC) listed adverse events and the Panel questioned whether in the absence of information in the consumer press release about side effects the press release was balanced.

The Panel noted that although the press articles referred to by the complainant did not report the confidence intervals for the results from Flaker *et al* and the RE-LY study, the press release did.

The Panel noted that the press release mentioned warfarin solely in relation to its use as a comparator in Flaker *et al* and the RE-LY studies. It did not refer to warfarin as rat poison and otherwise made no disparaging remarks about the medicine. The Panel had no evidence about how warfarin had been described by Boehringer Ingelheim's spokespersons or at any press conference. No breach of Clause 8.1 was ruled in that regard.

The Panel was concerned about the very positive statements in the 'Notes to Editors' section of the press release which described Pradaxa as 'leading the way in new oral anticoagulants/direct thrombin inhibitors …targeting a high unmet medical need' and queried whether this was a fair reflection of the evidence. The press release did not refer to Pradaxa as a 'super pill' or as a 'revolutionary drug'. These phrases only appeared in the press articles.

Overall the Panel was very concerned about the content of the press release and the briefing material for spokespersons. The Panel considered that these would in effect encourage members of the public to ask their health professional to prescribe a specific prescription only medicine. The Panel was concerned about the lack of

information in a consumer press release relating to side effects. A breach of Clause 22.2 was ruled. The Panel queried whether it was appropriate to issue the consumer press release relating to the unlicensed indication shortly before the grant of the authorization for that indication. The press release advertised a prescription only medicine to the public for an unlicensed indication. The Panel ruled a breach of Clause 22.1. The Panel considered that promotion of Pradaxa for an unlicensed indication was inconsistent with the terms of its marketing authorization. A breach of Clause 3.2 was ruled.

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

The material promoted a prescription only medicine to the public in an indication that was not yet licensed. The Panel noted that promotion prior to the grant of a marketing authorization was listed as an example of an activity that was likely to be in breach of Clause 2. Overall the Panel considered that the press release and the material for spokespersons brought discredit upon, and reduced confidence in, the industry. A breach of Clause 2 was ruled.

Complaint received	**16 May 2011**
Case completed	**15 July 2011**

GENERAL PRACTITIONER v BOEHRINGER INGELHEIM

Promotion of Pradaxa

A general practitioner alleged that the June 2011 edition of The British Journal of Cardiology contained disguised promotion of Pradaxa for the prevention of stroke/systemic embolism in patients with atrial fibrillation for which it was not licensed. Boehringer Ingelheim had applied to the European Medicines Agency (EMA) to extend the marketing authorization to include prevention of stroke and systemic embolism in atrial fibrillation.

The complainant noted that the news in brief section referred to the positive opinion issued by the EMA for Pradaxa for this unlicensed indication and the fact that this was based on the subgroup analysis of the Randomized Evaluation of Long-Term Anti-coagulant Therapy (RE-LY) study. The information about Pradaxa was indirectly linked to the back cover of the journal which featured a Boehringer Ingelheim advertisement entitled 'Stroke In Atrial Fibrillation'. It was clear that whilst Pradaxa was not mentioned, the advertisement was intended to allow readers to associate it with the information about Pradaxa referred to within the journal. The job code prefix ie DBG for dabigatran, for this advertisement also appeared in other Pradaxa promotional materials which further suggested that the advertisement was intended to be disguised promotion of Pradaxa.

The detailed response from Boehringer Ingelheim is given below.

In relation to the news items, the Panel noted that complaints about articles in the press were considered on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself.

The title of the first news item in the British Journal of Cardiology was 'Positive opinion for dabigatran in AF'. A press release issued by Boehringer Ingelheim, entitled 'Dabigatran etexilate (Pradaxa) recommended for approval in atrial fibrillation for stroke prevention in Europe', contained information about the positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for the use of dabigatran for stroke prevention in patients with atrial fibrillation. The press release also stated that this positive opinion was based on the results of the RE-LY study (Connolly *et al* 2009 and 2010). The Panel noted that the Notes to Editors section of the press release stated that dabigatran was not licensed in the UK for the prevention of stroke and systemic embolism in patients with atrial fibrillation. It also provided information about RE-LY.

The Panel considered that the medical media press release contained factual information about the EMA decision, and made it clear that dabigatran was not licensed for the prevention of stroke and systemic embolism. The Panel did not consider that the press release promoted dabigatran outside of the terms of its marketing authorization and ruled no breach.

The second news item in the British Journal of Cardiology was entitled 'RE-LY subgroup analysis reports' and stated that the results of an analysis of the RE-LY study showed that dabigatran was more effective than warfarin in stroke prevention for patients with atrial fibrillation, regardless of the risk of stroke. The news item was based on information provided by Boehringer Ingelheim in a second press release entitled 'Dabigatran etexilate provides consistent benefit across all atrial fibrillation types and stroke risk groups', which contained the results of two subgroup analyses of the RE-LY study (Flaker *et al* 2011 and Oldgren *et al* 2011) presented at the American College of Cardiology meeting. The press release stated that 150mg dabigatran twice a day was more effective to [*sic*] warfarin in stroke prevention in atrial fibrillation, irrespective of a patient's risk of stroke or type of atrial fibrillation.

Flaker *et al* noted that 150mg dabigatran twice daily was more effective than warfarin in stroke prevention across all atrial fibrillation types, and noted a similar rate with that dose to warfarin for major bleeding events. Oldgren *et al* noted that in patients with a low risk of stroke, both 110mg and 150mg dabigatran had lower rates of stroke, systemic embolism and major bleeding compared with warfarin.

The Panel considered that the press release accurately reflected the results of the two analyses in relation to the efficacy of dabigatran, although had concerns about the lack of detail in the press release in relation to side effects. The Panel did not consider that the press release promoted dabigatran outside of the terms of its marketing authorization and ruled no breach in that regard.

In relation to the advertisement that appeared on the back page of the same issue of the journal, the Panel noted that this was entitled 'Stroke in Atrial Fibrillation'. It contained an image of a lightening bolt striking a tree, the branches of

which resembled the outline of a human brain. The advertisement contained information about the occurrence and consequences of stroke in patients with atrial fibrillation. No reference, actual or implied, was made to any specific medicine. The Panel considered that the advertisement was a corporate advertisement about a disease and not about a specific medicine. The Panel did not consider that the fact that the advertisement at issue appeared in the same issue of the journal which reported on the new indication for dabigatran or the use of the code DBG meant that the advertisement promoted Pradaxa or constituted disguised promotion as alleged. The Panel did not consider that the advertisement promoted Pradaxa for an unauthorized indication and thus no breach was ruled. Nor did the advertisement in conjunction with the news articles constitute disguised promotion of Pradaxa and no breach was ruled in that regard.

The Panel noted its rulings above. It did not consider that Boehringer Ingelheim had failed to maintain high standards. Nor did it consider that the press releases and journal advertisement at issue brought discredit on, or reduced confidence in the pharmaceutical industry, and ruled no breach of the Code.

A general practitioner complained about the promotion of Pradaxa (dabigatran) by Boehringer Ingelheim Limited. Pradaxa was indicated for the primary prevention of venous thromboembolic events in adults who had undergone elective total hip or knee replacement surgery. Boehringer Ingelheim had applied to the European Medicines Agency (EMA) to extend the marketing authorization to include prevention of stroke and systemic embolism in atrial fibrillation.

COMPLAINT

The complainant alleged that the June 2011 edition of The British Journal of Cardiology (volume 18; issue 3) contained disguised promotion of Pradaxa for the prevention of stroke/systemic embolism in patients with atrial fibrillation.

The complainant noted that on page 111 of the journal, the news in brief referred to the positive opinion issued by the EMA for Pradaxa for this unlicensed indication and the fact that this was based on the subgroup analysis of the RE-LY study, which was also elaborated upon. Both of these items were based on a media briefing by Boehringer Ingelheim. The information about Pradaxa was indirectly linked to the back cover of the journal which featured a Boehringer Ingelheim advertisement (ref DBG 2420) entitled 'Stroke In Atrial Fibrillation'. It was clear that whilst Pradaxa was not mentioned, the advertisement was intended to allow readers to associate it with the information about Pradaxa referred to within the journal. The job code prefix ie DBG for dabigatran, for this advertisement also appeared in other Pradaxa promotional materials which further suggested that the advertisement was intended to be disguised promotion of Pradaxa.

When writing to Boehringer Ingelheim, the Authority asked it to respond in relation to Clauses 2, 3.2, 9.1 and 12.1 of the Code.

RESPONSE

Boehringer Ingelheim noted that news items which appeared on page 111 of the journal were brief. They consisted of two paragraphs over four column inches and reported upon the EMA positive opinion for dabigatran in atrial fibrillation and a single paragraph over one and a half column inches on the RE-LY subgroup analysis. The background to the placement of these articles was outlined in a letter from the British Journal of Cardiology dated 8 June 2011. The item reporting upon the positive opinion for dabigatran was compiled by the journal from information on the EMA website. Boehringer Ingelheim had issued a medical media release dated 18 April 2011 (ref DBG 2097) about this important announcement, a copy of which had been forwarded to the journal, but this was not the basis for the item. The item about the RE-LY study analyses reported at the American College of Cardiology was based upon a different Boehringer Ingelheim media release dated 5 April, 2011 (ref DBG 2368). Copies of both media releases were provided.

Both press releases related to new and important information about dabigatran; they presented the information accurately and without exaggeration. The company was committed to ensuring any information it issued complied with the Code.

The back cover of the journal carried a full page medical educational advertisement (ref DBG 2420), which noted the frequency of association of stroke and atrial fibrillation and the more negative outlook for those stroke patients with atrial fibrillation relative to those without. The advertisement did not refer to treatments and was not promotional.

Boehringer Ingelheim refuted the complainant's allegation that the advertisement was indirectly linked to the news items referred to above. The items were independent. Boehringer Ingelheim had no control over the editorial content of the journal. Although its agents had purchased space for the medical education advertisement, this was unrelated to any other coverage of dabigatran or other Boehringer Ingelheim interests. The letter from the British Journal of Cardiology strongly supported this position.

Boehringer Ingelheim noted the complainant's reference to the job code prefix 'DBG' which appeared on the advertisement as evidence that the advertisement was intended to be promotional. This was incorrect. A prefix and individual number was applied to all materials, whether promotional or not. The number was used for tracking purposes and its

inclusion did not indicate promotional activity or intent. Boehringer Ingelheim refuted the allegation that the advertisement was disguised promotion.

Boehringer Ingelheim denied that its conduct in relation to the recent press article brought discredit to, or reduced confidence in the industry. The company firmly asserted that it had behaved appropriately. Boehringer Ingelheim submitted that there was therefore no breach of Clause 2.

Boehringer Ingelheim noted that dabigatran was licensed for the primary prevention of venous thromboembolic events in adults who had undergone elective total hip or knee replacement surgery; it did not have a marketing authorization for stroke prevention in atrial fibrillation. This was made clear in both press releases which were factual and non-promotional. Boehringer Ingelheim thus denied a breach of Clause 3.2.

Boehringer Ingelheim considered that its conduct had been appropriate and complied with the Code and that high standards were maintained in the press releases. There was, therefore, no breach of Clause 9.1.

The advertisement was a medical educational item which had neither promotional content nor intent. As described above, the advertisement was unconnected with the brief news items published in the same issue of the journal. This was not disguised promotion and Boehringer Ingelheim thus denied a breach of Clause 12.1 of the Code.

Boehringer Ingelheim stated that on 15 April 2011 Pradaxa received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for the indication of stroke prevention in patients with atrial fibrillation based on the results of the RE-LY study. CHMP had recommended approval of Pradaxa in the member states of the EU for the: 'Prevention of stroke and systemic embolism in adult patients with nonvalvular AF with one or more of the following risk factors:

- Previous stroke, transient ischemic attack, or systemic embolism
- Left ventricular ejection fraction < 40%
- Symptomatic heart failure, ≥ New York Heart Association Class 2
- Age≥ 75 years
- Age≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension.

PANEL RULING

In relation to the news items, the Panel noted that complaints about articles in the press were considered on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself. The complaint was based on the news items.

The title of the first news item in the British Journal of Cardiology was 'Positive opinion for dabigatran in AF'. The Panel noted Boehringer Ingelheim's submission that the item was based on information that the journal had taken from the EMA website and not the medical media release issued by Boehringer Ingelheim. The Panel noted that the news item stated that the positive opinion was based on the RE-LY trial, which the EMA website made no reference to. This additional information was, however, included in the medical media press release dated 18 April issued by Boehringer Ingelheim in relation to the EMA's decision (DB2097).

The 18 April release was entitled 'Dabigatran etexilate (Pradaxa) recommended for approval in atrial fibrillation for stroke prevention in Europe', and contained information about the positive opinion from the CHMP for the use of dabigatran for stroke prevention in patients with atrial fibrillation. The press release also stated that this positive opinion was based on the results of the RE-LY study (Connolly *et al* 2009 and 2010). The Panel noted that the Notes to Editors section of the press release stated that dabigatran was not licensed in the UK for the prevention of stroke and systemic embolism in patients with atrial fibrillation. It also provided information about RE-LY.

The Panel considered that the medical media press release dated 18 April contained factual information about the EMA decision, and made it clear that dabigatran was not licensed for the prevention of stroke and systemic embolism. The Panel did not consider that the press release promoted dabigatran outside of the terms of its marketing authorization and ruled no breach of Clause 3.2

The second news item in the British Journal of Cardiology was entitled 'RE-LY subgroup analysis reports' and stated that the results of an analysis of the RE-LY study showed that dabigatran was more effective than warfarin in stroke prevention for patients with atrial fibrillation, regardless of the risk of stroke. The news item was based on information provided by Boehringer Ingelheim in the press release dated 5 April (DBG2368), entitled 'Dabigatran etexilate provides consistent benefit across all atrial fibrillation types and stroke risk groups', which contained the results of two subgroup analyses of the RE-LY study (Flaker *et al* 2011 and Oldgren *et al* 2011) presented at the American College of cardiology meeting. The press release stated that 150mg dabigatran twice a day was more effective to [sic] warfarin in stroke prevention in atrial fibrillation, irrespective of a patient's risk of stroke or type of atrial fibrillation.

Flaker *et al* noted that 150mg dabigatran twice daily was more effective than warfarin in stroke prevention across all atrial fibrillation types, and noted a similar rate with that dose to warfarin for major bleeding events. Oldgren *et al* noted that in patients with a low risk of stroke, both 110mg and 150mg dabigatran had lower rates of stroke, systemic embolism and major bleeding compared

with warfarin. The benefit of dabigatran 150mg versus warfarin was consistent across low, moderate and high risk patient groups with the absolute reduction in stroke or systemic embolism being the greatest in the highest risk group.

The Panel considered that the press release dated 5 April accurately reflected the results of the two analyses in relation to the efficacy of dabigatran, although had concerns about the lack of detail in the press release in relation to side effects. The Panel was also concerned about the very positive statements in the 'Notes to Editors' section of the press release which described Pradaxa as 'leading the way in new oral anticoagulants/direct thrombin inhibitors … targeting a high unmet medical need' and queried whether this was a fair reflection of the evidence. However, the Panel did not consider that the press release promoted dabigatran outside of the terms of its marketing authorization and ruled no breach of Clause 3.2.

In relation to the advertisement that appeared on the back page of the same issue of the journal, the Panel noted that this was entitled 'Stroke in Atrial Fibrillation'. It contained an image of a lightening bolt striking a tree, the branches of which resembled the outline of a human brain. The advertisement stated that at least 1 in 6 strokes occurred in patients with atrial fibrillation and that these patients were more likely to have a severe stroke with greater disability, have a longer in-hospital stays and a lower rate of discharge to their own homes, and were more likely to die from stroke. No reference, actual or implied, was made to any specific medicine. The Panel considered that the advertisement was a corporate advertisement about a disease and not about a specific medicine. The Panel noted Boehringer Ingelheim's submission in relation to having no control over the editorial content of the journal. The Panel did not consider that the fact that the advertisement at issue appeared in the same issue of the journal which reported on the new indication for dabigatran or the use of the code DBG meant that the advertisement promoted Pradaxa or constituted disguised promotion as alleged. The Panel did not consider that the advertisement promoted Pradaxa for an unauthorized indication and thus no breach of Clause 3.2 was ruled. Nor did the advertisement in conjunction with the news articles constitute disguised promotion of Pradaxa and no breach of Clause 12.1 was ruled.

The Panel noted its rulings above. It did not consider that Boehringer Ingelheim had failed to maintain high standards, and ruled no breach of Clause 9.1. The Panel did not consider that the press releases and journal advertisement at issue brought discredit on, or reduced confidence in the pharmaceutical industry, and ruled no breach of Clause 2.

Complaint received	**6 June 2011**
Case completed	**22 July 2011**

CASE AUTH/2409/6/11

ANONYMOUS v CEPHALON

Qualifications of medical signatory

An anonymous non-contactable complainant who described themselves as an ex-employee of Cephalon UK complained that a medical affairs manager with signatory and approval powers was not a qualified doctor.

The detailed response from Cephalon is given below.

The Panel noted that the 2008 Code which applied at the time in question required that, *inter alia,* promotional material must not be issued unless it had been certified by two signatories one of which had to be a registered medical practitioner. The Code did not require the medical practitioner to be registered in the UK but the Authority advised that proposed medical signatories should be capable of being registered in the UK without the need for additional tests of medical/clinical knowledge. There were no requirements in the Code relating to the actual qualifications of medical signatories. The supplementary information stated that in deciding whether a person could be a nominated signatory account should be taken of product knowledge, relevant experience, both within and outwith the industry, length of service and seniority. In addition, signatories must have an up-to-date detailed knowledge of the Code.

The Panel noted that Cephalon had provided a job description to the recruitment agency to identify suitable candidates for the role of interim medical advisor. The job description made it clear that candidates should be medically qualified with current GMC registration and at least 2 years post registration clinical experience. Cephalon submitted that the person in question had undertaken roles within major UK pharmaceutical companies which in its view would have required GMC registration. Cephalon's standard operating procedure (SOP) required that the final medical signature must be a registered medical practitioner and although the person in question completed training on this SOP he did not advise Cephalon of the position. It was only when Cephalon made checks for recruiting a permanent role that it was discovered that the person in question was not GMC registered.

The Panel noted that in the five months he had worked for Cephalon approximately 45 items had been certified by him. These items were reviewed at that time internally by medical and other experienced Code signatories. Following the departure of the person in question Cephalon reviewed all the items which had been certified by him and submitted that they were of good quality and compliant with the Code.

The Panel considered that there was the possibility that although not GMC registered the person in question was registered as a medical practitioner in another country. The person in question did not indicate to Cephalon that this was so. The Panel considered that in the initial temporary appointment Cephalon had been badly let down by the recruitment agency. However materials had been certified by someone whom Cephalon could not show was a registered medical practitioner. The requirements of the Code had not been met and thus the Panel ruled a breach of the Code as acknowledged by Cephalon.

The Panel noted that the person in question had been trained on Cephalon's SOPs and had received regular updates on the Code from an external agency. No evidence was provided by the complainant to show that the person in question had not received training. The Panel ruled no breach of the Code.

Taking all the circumstances into account, including the requirement from Cephalon that signatories were GMC registered, the Panel considered that on balance Cephalon had not failed to maintain high standards. No breach of the Code was ruled. The Panel did not consider the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and thus no breach of that clause was ruled.

An anonymous non-contactable complainant who described themselves as an ex-employee of Cephalon UK complained about the qualifications and role of a medical affairs manager previously employed by Cephalon.

The complainant was considered under the Constitution and Procedure of the 2011 edition of the Code and in relation to the requirements of the 2008 Code.

COMPLAINT

The complainant stated that the medical affairs manager was employed by Cephalon between 2009 and 2010 and during this time he had signatory and approval powers. It later transpired that he actually was not a qualified doctor.

Whilst mistakes could occur, on this occasion it

appeared that Cephalon senior management was negligent in its duty in ensuring that all reasonable checks were made and as such left all employees at risk in terms of compliance with the Code.

The complainant advised that although he had now left Cephalon, the gravity of this situation had compelled him to write to try and ensure that correct procedures were put in place and acted upon to avoid a repeat of this incident.

Cephalon was asked to respond in relation to the requirements of Clauses 2, 9.1, 14.1 and 16.1 of the 2008 Code.

RESPONSE

Cephalon explained that in September 2009 a job description for a medical advisor was sent from Cephalon UK to a recruitment agency to identify suitable candidates to fill the role for an interim medical advisor. The agency in question was selected due to its particular expertise and specialism in recruiting physicians both for the pharmaceutical industry and for the NHS.

Cephalon drew attention to four key elements highlighted within the job description:

1 The overall role purpose was to provide 'comprehensive medical advisor support to the UK affiliate in accordance with local regulations and the Code of Practice'

2 A key activity was to 'Input to, review and approve promotional materials to Company, UK legal, and ABPI standards'

3 One of the typical outputs was 'Approved promotional materials'

4 The technical/professional expertise required of the job holder included that the person was 'Medically qualified with current GMC registration and at least 2 years post-registration clinical experience'.

The role reported directly to the Cephalon UK medical director, who was GMC registered and also the hiring manager.

Cephalon UK received a curriculum vitae (CV) for the individual in question from the agency. The CV referred to BSc in Clinical Science from Imperial College London, a medical degree from Imperial College London and membership of the Royal College of Psychiatrists. The person in question had undertaken a variety of roles in the NHS to the level of senior registrar at prominent UK hospitals. Within the pharmaceutical industry, he had undertaken medical roles within three major UK pharmaceutical companies as a clinical research physician and as a medical adviser/senior medical adviser, roles which would have required GMC registration.

A contract for services as an interim medical advisor was signed between the agency and Cephalon UK and the person in question commenced working at Cephalon in late 2009. The person in question was not employed directly by Cephalon UK at any point, but was an independent medical consultant employed via the agency.

As part of the normal process for training of new staff (including contracted staff) the person in question underwent training on a number of Cephalon UK standard operating procedures (SOPs) which were relevant to the Code, as well as numerous other Cephalon SOPs of broader relevance to his role. The person in question on completion of this training, was monitored using an online compliance system which was common to the entire company. One of these SOPs referred to approval of promotional materials and training on this was completed in 2009. The SOP required that the final medical signature must be a registered medical practitioner, and although the person in question completed the training, he did not advise of his deficiency with respect to this.

The person in question also received regular updates on recent cases and key points arising from those cases via an external agency, which specialised in healthcare compliance and codes of practice. This agency provided an update service specifically for Code signatories which the person in question received regularly during his employment.

Following satisfactory spring performance the person in question was offered permanent employment at Cephalon in 2010 subject to satisfactory pre-employment checks.

As part of the normal process for recruitment of permanent staff, further diligence was undertaken by the HR department including obtaining evidence of previous employment (via references from previous employers), evidence of academic qualifications and GMC registration status. At this point, it was discovered that the person in question was not registered with the GMC. The offer of employment was withdrawn and the person in question's employment as a contractor was terminated immediately.

The person in question had been a final Code signatory during the short time he was employed at Cephalon, and he had signed off approximately 45 promotional items. These were reviewed at that time internally by medical and by other experienced Code signatories at Cephalon.

Cephalon's management was naturally extremely concerned about this lack of GMC registration, and an experienced external consultant pharmaceutical physician with 25 years of experience in the pharmaceutical industry was also employed as a matter of urgency to examine the promotional materials that had been signed by the person in question. The external medical consultant confirmed that these were Code compliant, had

been approved to a high standard and that at no time had the sales force been using non-compliant or misleading promotional materials.

The three Cephalon managers who at that time were involved in the recruitment of the person in question were no longer employed by Cephalon UK and it had been unable to obtain additional information from these individuals before responding to the complaint.

In common with many pharmaceutical companies in the UK, Cephalon was occasionally obliged to employ external contractors to fill short-term vacancies and relied upon third parties to source such staff. Section 10.1 of the contract with the agency indicated that it should 'use its best endeavours to ensure that the consultant [the person in question] possesses the skill, experience, reliability, and integrity necessary to properly provide the consultancy services'.

However, Cephalon acknowledged that it must take responsibility for this deficiency and therefore accepted that high standards at that time were not maintained in breach of Clause 9.1.

With respect to the requirements of Clause 16.1, the person in question was specifically trained on company SOPs relevant to the Code and received regular updates about the Code. The findings of the physician employed to examine the promotional items he approved found them to be of good quality. On this basis, Cephalon did not accept a breach of Clause 16.1.

Cephalon accepted also that at that time an error of omission occurred in that the agency failed to highlight the lack of GMC registration despite the fact that this was an absolute requirement of the job description. Cephalon had subsequently changed its procedures to ensure that the GMC status of any physician employed at the company was checked prior to commencing employment, irrespective of whether the employee in question was permanent or externally-contracted. Cephalon also appreciated the serious nature of this matter, and was aware of the potential implications for certification of promotional materials by inappropriate individuals.

Given its action on discovering the situation Cephalon did not accept the complainant's assertions of mismanagement and did not accept a breach of Clause 2.

In response to a request for further information in relation to Clause 14.1 Cephalon stated that the provisions of Clause 14.1 had not been met with regard to the requirement for final certification by a registered medical practitioner, and Cephalon accepted a breach of this Clause.

In respect of the person in question's registration, Cephalon discovered that he was not GMC registered in spring 2010. In addressing the supplementary question as to whether the person in question was capable of being registered at that time, the company had undertaken extensive inquiries via the GMC online registration facility, but had not found an individual who was on the register who matched the person in question's name and stated qualifications. Further direct communication with the GMC had also failed to elicit a match given the information the company had available. Cephalon was therefore not able to give a definitive answer to the question in relation to his capability of being GMC registered.

The person in question did not indicate to Cephalon that he was registered in another jurisdiction and the company had had no communication with him since he had stopped working at Cephalon. It had not received any further information relevant to these matters from the recruitment agency in question.

PANEL RULING

The Panel noted that Clause 14.1 of the 2008 Code which applied at the time in question required that, *inter alia,* promotional material must not be issued unless it had been certified by two signatories one of which had to be a registered medical practitioner. Clause 14.1 also allowed a practising UK registered pharmacist working under the direction of a registered medical practitioner to certify certain material as set out in Clause 14.1. The Code did not require the medical practitioner to be registered in the UK but the Authority advised that proposed medical signatories should be capable of being registered in the UK without the need for additional tests of medical/clinical knowledge. There were no requirements in the Code relating to the actual qualifications of medical signatories. The supplementary information stated that in deciding whether a person could be a nominated signatory account should be taken of product knowledge, relevant experience, both within and outwith the industry, length of service and seniority. In addition, signatories must have an up-to-date detailed knowledge of the Code.

The Panel noted that Cephalon had provided a job description to the recruitment agency to identify suitable candidates for the role of interim medical advisor. The job description made it clear that candidates should be medically qualified with current GMC registration and at least 2 years post registration clinical experience. Cephalon submitted that the person in question had undertaken roles within 3 major UK pharmaceutical companies which in its view would have required GMC registration. Cephalon's SOP required that the final medical signature must be that of a registered medical practitioner and although the person in question completed training on this SOP he did not advise Cephalon of the position. It was only when Cephalon made checks for recruiting the person in question to a permanent role that it was discovered that he was not GMC registered and the offer of employment was withdrawn and the person in question dismissed.

The Panel noted that in the five months he had worked for Cephalon approximately 45 items had been certified by him. These items were reviewed at that time internally by medical and other experienced Code signatories. Following the departure of the person in question Cephalon reviewed all the items which had been certified by him and submitted that they were of good quality and compliant with the Code.

The Panel considered that there was the possibility that although not GMC registered the person in question was registered as a medical practitioner in another country. The person in question did not indicate to Cephalon that this was so. The Panel considered that in the initial temporary appointment Cephalon had been badly let down by the recruitment agency. However materials had been certified by someone whom Cephalon could not show was a registered medical practitioner. The requirements of Clause 14.1 had not been met and thus the Panel ruled a breach of that clause as acknowledged by Cephalon.

In relation to the requirements of Clause 16.1, the Panel noted that the person in question had been trained on Cephalon's SOPs and had received regular updates on the Code from an external agency. No evidence was provided by the complainant to show that the person in question had not received training as required by Clause 16.1. The Panel ruled no breach of that clause.

Taking all the circumstances into account, including the requirement from Cephalon that signatories were GMC registered, the Panel considered that on balance Cephalon had not failed to maintain high standards . No breach of Clause 9.1 was ruled. The Panel did not consider the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and thus no breach of that clause was ruled.

Complaint received **16 June 2011**

Case completed **26 July 2011**

ANONYMOUS v LILLY

Provision of Byetta samples

An anonymous, non contactable complainant who described themself as a concerned member of staff at a named hospital complained about the distribution of Byetta (exenatide) samples by Eli Lilly and Company. The complainant alleged that Lilly had placed a large number of samples of Byetta in the pharmacy at the hospital to encourage doctors to prescribe it. The aim was to encourage use of Byetta at the hospital as initial prescriptions of Byetta would effectively be provided free of charge to patients with diabetes. The complainant did not consider this was correct practice as even if this reduced medicines costs for the hospital, doctors were being led to use an expensive medicine the cost of which would be picked up later in primary care.

The detailed response from Lilly is given below.

The Panel noted Lilly's submission that its sales representative received a request to provide samples from the lead pharmacist on behalf of the hospital pharmacy diabetes and metabolism departments. It was unclear whether it was a verbal or written request. Ten samples each were provided to four physicians. In this regard the requirements of the Code had been met and no breach was ruled. The Panel noted Lilly's submission that Byetta had received its marketing authorization in November 2006 and had thus been on the market for less than 10 years; a further ruling of no breach of the Code was ruled on this point.

The Panel noted that each sample request form had been signed and dated by the applicant as required by the Code and a further ruling of no breach was ruled.

The Panel noted that the lower section of Lilly's sample request form entitled 'Hospital Pharmacy Contact Details' required the hospital pharmacy to confirm that the supply of samples requested by the doctor named on the form complied with hospital requirements on samples. The section on the forms at issue had been signed and dated by the purchasing pharmacist on 2 February 2011 whereas each of the requesting clinicians had subsequently signed between 8 and 11 February. The forms were thus not countersigned by the purchasing pharmacist as submitted by Lilly. The Panel queried whether the pharmacist should have signed four forms on which the clinician's name had been printed but which did not bear the clinician's signature. According to Lilly, the number of samples was stated on the form when it was signed by the pharmacist. The hospital policy provided by Lilly stated in relation to samples that representatives must not leave samples with individual clinicians or staff. If a clinician wished to try a particular medicine this must be through prior arrangement with the pharmacy department and the relevant committees. The hospital policy was silent on the signing and completion of sample request forms. It was unclear whether the policy provided was indeed the latest version. In this regard the Panel noted that it was unfortunate that the complainant was anonymous and non contactable and thus it was not possible to ask him/her for further information. Irrespective of its concerns set out above the Panel considered that there was no evidence that the provision of samples had failed to comply with the hospital's requirements as set out in the policy document provided. No breach of the Code was ruled accordingly.

The Panel noted the complainant's comments about the cost of the product when the patient transferred to primary care. There was no evidence before the Panel that the samples were provided as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine contrary to the Code and no breach was ruled.

The Panel noted its rulings of no breaches of the Code above and consequently did not consider that the company had failed to maintain high standards or brought the industry into disrepute; no breaches of the Code were ruled.

An anonymous, non contactable complainant who described themself as a concerned member of staff at a hospital complained about the distribution of Byetta (exenatide) samples by Eli Lilly and Company Limited.

COMPLAINT

The complainant stated that Lilly had placed a large number of samples of Byetta in the pharmacy at his hospital to encourage doctors to prescribe it. The aim was to encourage use of Byetta at the hospital as initial prescriptions of Byetta would effectively be provided free of charge to patients with diabetes.

As a member of staff the complainant did not consider this was correct practice. Lilly should not have placed these samples into a hospital free of charge. Even if this reduced medicines costs for the hospital, doctors were being led to use an expensive medicine the cost of which would be picked up later in primary care.

When writing to Lilly, the Authority asked it to

respond in relation to Clauses 17.2. 17.3, 17.8, 17.12, 9.1 and 2 of the Code.

RESPONSE

Lilly stated that it had examined its records for the supply of Byetta to the hospital in question over the past year and believed its activities were in compliance with Clause 17 (other than Clause 17.6 which was not applicable), Clauses 2 and 9.1.

Lilly stated that its sales representative received the original request from the lead pharmacist on behalf of the pharmacy and diabetes and metabolism departments at the hospital in January 2011 to provide samples of Byetta for each (physician) prescriber in the diabetes department (Clause 17.1). The purpose of the request was to allow prescribers in the diabetes department 'to develop their limited clinical experience in the use of this product for each prescriber in the department' before the patient left hospital (Clause 17.12). Four physicians completed the relevant sample supply documentation to receive samples (a maximum of 10 samples each over the year, 40 samples in total – Clause 17.2) in February 2011. All forms were completed in full with signatures and General Medical Council numbers. The requests were countersigned by the purchasing pharmacist to confirm compliance with hospital's requirements for the supply of samples (Clauses 17.3 and 17.8). A copy of the policy was provided together with copies of the request forms. These requests were recorded as submitted and supplied on the Lilly supply database during February 2011 (Clause 17.9).

Byetta received a marketing authorization in November 2006 and had been on the UK market for less than 10 years (Clause 17.2). Each sample comprised a Byetta pre-filled pen 5mcg dose (the smallest presentation of the product on the market, Clause 17.4) and was marked 'sample' (Clause 17.5). Clauses 17.7, 17.10 and 17.11 were complied with in the distribution process.

Lilly submitted that the evidence outlined demonstrated that it had complied with all requirements of the Code. It therefore disputed the complainant's allegations that it had supplied a large number of samples to encourage doctors to supply this product as the samples were supplied free of charge.

In response to a request for further information Lilly explained that diabetologists from the department of diabetes had expressed their wish to gain experience with this group of medicines and specifically asked its representative for Byetta samples. The local hospital core policy guideline for provision of samples, stated that 'prior arrangements with the Pharmacy Department' must be put in place. Sample request forms stating the name of the physicians and the number of samples requested were then authorised by the purchasing pharmacist on 2 February 2011. Individual physicians already named on the request forms subsequently signed the documents between 8 and 11 of February 2011.

In response to a further request for information about the dates recorded in the database document Lilly explained that a third party company managed the delivery of its samples. The date of the sample request on the database document referred to the date of signatures either by the purchasing pharmacist or the requesting doctor presumably reflecting different handling of these documents by the company. All samples were dispatched between 17 and 21 of February 2011.

Lilly considered that the evidence outlined above demonstrated that it had complied with all requirements of the Code in terms of the supply of samples of Byetta to the hospital diabetes department in February, 2011. Lilly therefore disputed the contentions made in the anonymous complaint that it had supplied a large number of samples to encourage doctors to supply Byetta as the samples were supplied free of charge.

PANEL RULING

The Panel noted that the complainant was concerned that Lilly had placed Byetta samples at the hospital pharmacy to encourage doctors to prescribe it. The complainant noted that whilst there would be a cost saving for the hospital the cost of the medicine, which the complainant considered expensive, would subsequently be picked up in primary care. The Panel noted that the provision of samples was a legitimate activity so long as the requirements of the Code, and in particular Clause 17, were met.

The Panel noted that according to its summary of product characteristics (SPC) Byetta therapy should be initiated at a dose of 5mcg twice daily for at least one month in order to improve tolerability. The dose could then be increased to 10mcg twice daily to further improve glycaemic control. The Panel noted that each pre-filled pen contained 60 doses and thus enough for one month's supply for a new patient. The Panel noted the definition of a sample in the supplementary information to Clause 17.1 and queried whether, given the requirement to administer the product for at least one month before any dose adjustment, together with the fact that the patient would be transferred to the care of their GP before completing the first month of therapy, a hospital doctor would genuinely acquire meaningful experience in dealing with the product. The Panel noted Lilly's submission that the samples would allow each prescriber to develop their limited clinical experience in the use of the product before the patient left hospital.

The Panel noted Lilly's submission that its sales representative received a request to provide samples from the lead pharmacist on behalf of the hospital pharmacy diabetes and metabolism departments. It was unclear whether it was a verbal or written request. Ten samples each were provided

to four physicians. In this regard the requirement of Clause 17.2 had been met; no breach of Clause 17.2 was ruled. The Panel noted Lilly's submission that Byetta had received its marketing authorization in November 2006 and had thus been on the market for less than 10 years; a further ruling of no breach of Clause 17.2 was ruled.

The Panel noted that each sample request form had been signed and dated by the applicant as required by Clause 17.3. No breach of Clause 17.3 was thus ruled.

The Panel noted that the lower section of Lilly's sample request form entitled 'Hospital Pharmacy Contact Details' required the hospital pharmacy to confirm that the supply of samples requested by the doctor named on the form complied with hospital requirements on samples. The section on the forms at issue had been signed and dated by the purchasing pharmacist on 2 February 2011 whereas each of the requesting clinicians had subsequently signed between 8 and 11 February. The forms were thus not countersigned by the purchasing pharmacist as submitted by Lilly. The Panel queried whether the pharmacist should have signed four forms on which the clinician's name had been printed but which did not bear the clinician's signature. According to Lilly, the number of samples was stated on the form when it was signed by the pharmacist.

The hospital policy provided by Lilly stated in relation to samples that representatives must not leave samples with individual clinicians or staff. If a clinician wished to try a particular medicine this must be through prior arrangement with the pharmacy department and the relevant committees. The hospital policy was silent on the signing and completion of sample request forms. The front page of the hospital policy bore approval and adoption dates of November 2004 and April 2008. It also referred to a review in April 2011. A section within the policy document was dated 3 July 2008 in relation to an unrelated matter. It was unclear whether the policy provided was indeed the latest version. In this regard the Panel noted that it was unfortunate that the complainant was anonymous and non contactable and thus it was not possible to ask him/her for further information. Irrespective of its concerns set out above the Panel considered that there was no evidence that the provision of samples had failed to comply with the hospital's requirements as set out in the policy document provided. No breach of Clause 17.8 was ruled accordingly.

The Panel noted the complainant's comments about the cost of the product when the patient transferred to primary care. There was no evidence before the Panel that the samples were provided as an inducement to prescribe supply, administer, recommend, buy or sell any medicine contrary to Clause 17.12. No breach of Clause 17.12 was ruled.

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

Complaint received	**24 June 2011**
Case completed	**20 July 2011**

CASE AUTH/2413/6/11

VOLUNTARY ADMISSION BY LEO

Promotion of Xamiol to the public

Leo Pharma advised that a film clip which demonstrated the application of Xamiol Gel (calcipotriol/betamethasone) on scalp psoriasis had been included on a DVD produced by Biogen Idec and distributed to health professionals and patients. In accordance with the Constitution and Procedure for the Prescription Medicines Code of Practice Authority, the Director treated the matter as a complaint. (The Director also took the matter up with Biogen Idec – see Case AUTH/2415/6/11).

Biogen Idec informed Leo that a Tysabri (natalizumab) patient DVD had been distributed that contained this film clip. The DVD was originally approved in April 2010 and DVDs without any error were produced by one production company. In March 2011 production was switched to a new agency and DVDs were produced which contained the Xamiol film clip. Leo had been informed that Biogen Idec would recall all the DVDs from health professionals and representatives but it did not plan a recall from patients. The Xamiol film clip in question arrived at the agency in December 2010 from Leo's Head Office in Denmark. Leo's Head Office had a confidentiality agreement with the agency which included instructions for destruction of materials.

The detailed response from Leo is given below.

According to Leo, Biogen Idec had explained that the video clip had appeared on its DVD as a result of an error post-certification at the agency. The Panel noted that the agency had the video clip as a result of its contract with Leo's headquarters.

The DVD in question had been distributed by Biogen Idec to patients. Leo's prescription only medicine had thus been promoted to the public and the Panel ruled a breach of the Code.

The Panel considered that Leo had been badly let down by the agency. Overall the Panel considered that Leo had not failed to maintain high standards and no breach of the Code was ruled. Consequently, the Panel ruled no breach of Clause 2.

Leo Pharma advised that a Xamiol (calcipotriol/betamethasone) film clip had appeared on a DVD distributed by Biogen Idec Limited to patients. In accordance with Paragraph 5.6 of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority, the Director treated the matter as a complaint.

The Director also took the matter up with Biogen Idec (Case AUTH/2415/6/11).

COMPLAINT

A film clip demonstrating the application of Xamiol Gel on scalp psoriasis included on a DVD produced by Biogen Idec Ltd and distributed to health professionals and patients had recently come to Leo's attention.

Biogen Idec informed Leo that a Tysabri (natalizumab) patient DVD had been distributed that contained a Xamiol film clip. Apparently, this piece was originally approved by Biogen Idec in April 2010 and DVDs without any error were produced by one production company. In March 2011 production of the Tysabri DVD was switched to a new agency which produced 1,014 DVDs containing the Xamiol production film clip; 760 of these DVDs were still in the warehouse. Of the remaining 254, Leo had been informed that Biogen Idec would recall all the DVDs from health professionals and representatives but it did not plan a recall from patients.

The Xamiol film clip in question arrived with the agency in December 2010 from Leo Head Office in Denmark. Leo's Head Office had a confidentiality agreement in place with the agency which included instructions for destruction of materials. A copy of the film clip on a DVD was provided.

When writing to Leo, the Authority asked it to respond in relation to Clauses 22.1, 9.1 and 2 of the Code.

RESPONSE

Leo stated that it became aware of the incident through a courtesy call from Biogen Idec on 15 June 2011. Biogen Idec advised that a promotional video clip of Xamiol had inadvertently been included on a Biogen Idec Tysabri patient DVD destined to be distributed to health professionals and patients.

Leo immediately started to contact those involved in the production of the Biogen Idec DVD to establish as many facts as possible and so determine the appropriate course of action to minimize any potential hazard to patients.

The Xamiol video clip in question was sent to the agency in November 2010 by Leo Head Office in Denmark. It had never been used in the UK.

On 16 June Leo contacted both parties known to have been involved in the production of the Biogen DVD, the agency and Biogen Idec.

Leo requested and obtained on 17 June a video clip of Xamiol as it appeared on the Biogen Idec DVD

but isolated from the Tysabri patient DVD. In the absence of the original defective DVD, Leo was unable to provide any further information on the point of integration of the Xamiol material. The Biogen Idec patient DVD contained the Xamiol video clip without the inclusion of prescribing information or adverse event reporting advice when given to health professionals and potentially promoted the product directly to patients.

Leo understood that 1,014 DVDs were produced in February 2011 by the agency, 760 were still in a warehouse, so the remaining 254 DVDs were assumed to have been distributed. The total number of defective DVDs was unknown. The agency suggested that all DVDs were defective since they would have all been made from the original master file. Biogen Idec suggested that the Xamiol material inclusion was only on very limited copies and suggested that the error occurred post certification during manufacture. In the absence of access to the master file of the Biogen Idec DVD, Leo had no means to estimate the actual number of defective DVDs. The company insisted that all DVDs be recalled and destroyed forthwith and requested a copy of the destruction certificate.

Corrective action proposed and initiated by Biogen Idec was that the DVD was recalled from health professionals and Biogen Idec representatives but not from patients. Leo did not know the timeline of the recall. Leo stated that its request for further information from Biogen Idec confirming the recall timeline and destruction, by 22 June remained unanswered.

Leo submitted that it had self reported the matter due to the risk of promotion to patients along with inadequate information alongside the product when provided to health professionals. Leo had no means of establishing where the items had been distributed and hence was unable to account for recall of each item.

Clause 22.1 prohibited advertising prescription only medicines to patients. As outlined above the Xamiol video clip was inadvertently included in the Tysabri patient DVD, without any permission from Leo to do so or Leo having any knowledge of this use of the Xamiol clip. Leo believed that this fact, together with its request for immediate recall and destruction of all defective materials, demonstrated that it was not in breach of Clause 22.1 of the Code.

Leo was confident that it had taken all steps possible and necessary to ensure that the Xamiol promotional material distributed without its knowledge was recalled and destroyed. Moreover, it had made a voluntary submission about the matter to ensure transparency in all its promotional activities, therefore maintaining the high standards for the promotion of medicines expected from pharmaceutical companies under Clause 9.1.

To ensure that patient safety or patient health was not compromised as outlined in Clause 2, Leo insisted on the recall of all defective DVDs from patients not just health professionals as suggested by Biogen Idec. Leo submitted that this demonstrated its commitment to the Code as a whole and supported its understanding that Leo's actions specifically demonstrated it did not breach Clause 2.

PANEL RULING

The Panel noted that Clause 22.1 prohibited the promotion of a prescription only medicine to the public. Leo explained that the Xamiol video clip had been sent directly to the UK agency by Leo's headquarters in Denmark. The video clip at issue had never been distributed by Leo in the UK. However, given that the DVD in question was distributed in the UK, albeit by a different company, the Panel considered that Leo, based in the UK, was responsible for this matter under the Code.

According to Leo, Biogen Idec had explained that the video clip had appeared on its DVD as a result of an error post-certification at the agency. The Panel noted that the agency had the video clip as a result of its contract with Leo's headquarters. It was a well established principle that a company was responsible for the acts or omissions of its agents or third parties. If this were not the case companies would be able to rely on such acts or omissions as a means of circumventing the requirements of the Code. Leo was thus responsible for the acts or omissions of the agency in relation to the video clip.

The DVD in question had been distributed by Biogen Idec to patients. Leo's prescription only medicine had thus been promoted to the public and the Panel ruled a breach of Clause 22.1.

The Panel acknowledged the corrective action taken promptly by Leo once it had been informed by Biogen Idec of the error. The Panel noted that a confidentiality agreement had been in place between Leo's headquarters and the agency which included instructions for destruction of materials. The Panel had not seen a copy of the agreement nor did it know whether a certificate of destruction had been requested by Leo's headquarters. In any event, the Panel considered that Leo had been badly let down by the agency. Overall the Panel considered that Leo had not failed to maintain high standards and no breach of Clause 9.1 was ruled. Consequently, the Panel ruled no breach of Clause 2.

Proceedings commenced	**24 June 2011**
Case completed	**5 August 2011**

CASE AUTH/2415/6/11

DIRECTOR v BIOGEN IDEC

Tysabri DVD

Leo Pharma advised the Authority that a Tysabri (natalizumab) DVD produced and distributed by Biogen Idec to health professionals and patients included a film clip demonstrating Leo's product Xamiol Gel (calcipotriol/betamethasone) on psoriasis (Case AUTH/2413/6/11). It thus appeared that Xamiol Gel, a prescription only medicine, might have been advertised to the public. In accordance with the Authority's Constitution and Procedure this matter was taken up with Biogen Idec as as a complaint under the Code.

The detailed response from Biogen Idec is given below.

The Panel noted that due to human error on a production run at a third party DVD manufacturer, promotional material for Xamiol had been placed on a DVD provided to patients who had been prescribed Tysabri.

A prescription only medicine had thus been promoted to the public, and the Panel ruled that Biogen Idec was in breach of the Code.

The Panel noted that Biogen Idec had certified the DVD in question in August 2010. Biogen Idec had engaged a different company to manufacture the DVD in 2011. The Panel noted that the manufacturing process involved uploading the approved electronic file on to the DVD; a process which was open to human error. The Panel noted the risk of human error and the serious consequences if such risk materialized in relation to material directed at patients. The Panel considered it would have been good practice for Biogen Idec, prior to distribution, to have checked a DVD from the production run against that certified by the company.

The Panel considered that the quality checks that Biogen Idec put in place as a result of this complaint should have been in place from the outset. These checks were particularly important when the material produced was intended for patients. High standards had not been maintained, and a breach of the Code was ruled.

The Panel did not consider that the circumstances brought discredit upon or reduced confidence in the pharmaceutical industry and no breach of Clause 2 was ruled.

The Director received information from which it appeared that Biogen Idec Limited might have contravened the Code. Paragraph 5.1 of the Constitution and Procedure for the Authority required that such a matter was taken up as a formal complaint under the Code.

COMPLAINT

Leo Pharma advised the Authority that a Tysabri (natalizumab) DVD produced and distributed by Biogen Idec to health professionals and patients included a film clip demonstrating Leo's product Xamiol Gel (calcipotriol/betamethasone) on psoriasis (Case AUTH/2413/6/11). It thus appeared that Xamiol Gel, a prescription only medicine might have been advertised to the public.

Biogen Idec was asked to respond in relation to Clauses 22.1, 9.1 and 2 of the Code.

RESPONSE

Biogen Idec confirmed that it had no conflicts of interest in this matter. Leo and Biogen Idec UK operated in different therapeutic areas (dermatology and neurology respectively), and were not competitors.

On Thursday, 9 June 2011, a Biogen Idec representative noted that a Tysabri DVD entitled 'A guide to MS [multiple sclerosis] and how Tysabri works' (TY-PAN-0177c April 2010) contained a 54 second video demonstrating the application of Leo's Xamiol Gel. The representative immediately notified Biogen Idec and returned the DVD. There was no narrative to accompany the video. The DVD was packaged in a DVD case (TY-PAN-0177d). No Tysabri material was present on the copy of the erroneous DVD.

The Tysabri DVD was intended to be provided to patients who had already been prescribed Tysabri by their health professionals. It contained factual information regarding Tysabri, multiple sclerosis, the infusion method for delivery, potential side effects, patient experiences and sources of further information.

The DVD was initially reviewed and certified in November 2008 via hard copy job bag (TY-PAN-23515 DVD). The Tysabri DVD was created and manufactured by an agency on behalf of Biogen Idec. The job bag was subsequently archived.

The Tysabri DVD was initiated for a re-review in April 2010, and reviewed/certified in August 2010 (TY-PAN-0177c) to incorporate updated product safety information. The DVD was provided to health professionals by representatives after 24 August 2010.

During the first quarter of 2011, production of the DVD and case was transferred to a new manufacturing vendor. This agency sub-contracted manufacture of the DVD disk. Both the current agency and the sub-contracted manufacturer were ISO9001 accredited. The content of the DVD was intended to be unchanged from the approved version, and no instruction was provided for the manufacturer to alter content.

The erroneous DVD in question related to the first and only production run of 1,015 DVDs manufactured by the sub-contracted agency. The DVDs were shipped from the manufacturer to the warehouse on 10 March 2011, and thence to representatives from 14 March 2011 onwards. Of the 1,015 DVDs, 738 remained in the warehouse. To date, Biogen Idec had not been notified of any other erroneous copies of this DVD. Once the error was detected on 9 June, a product recall process was immediately put in place to start the recall of all DVDs from all representatives and their return to the warehouse for destruction. All DVDs were dispatched to the warehouse for destruction by Monday 13 June (together with the remaining warehouse stock of 738 DVDs which were retained for destruction).

The previous and the current agency were contacted on 13 June and asked to conduct an internal investigation to determine how the error had occurred. A teleconference was held with both agencies on Wednesday 15 June to share feedback from the investigation. It was suspected that due to human error at the sub-contracted manufacturer the incorrect Xamiol file had been uploaded onto the Tysabri DVD. To date, Biogen Idec had not been notified of any erroneous copies of this DVD in the field other than the single copy notified by a representative on 9 June. The company was informed by the manufacturer that the error might not be universally apparent. This might explain why it had not been informed of further erroneous DVDs from patients or health professionals, nevertheless Biogen Idec took the precaution of recalling all relevant materials. It was possible that the mistake was an isolated case although this could not be verified by the manufacturer.

Leo was contacted on Wednesday 15 June to inform it of the incident, and Biogen Idec's actions to date. A further summary of actions was provided to Leo on 17 June. A copy of the affected DVD was couriered to Leo on the same day. Further calls were held with Leo during the following week.

On Monday 20 June a briefing document was sent to all UK representatives asking them to contact each clinic which might have been given copies of the DVD and collect any that the clinic had in stock for destruction (irrespective of DVD content). Clinics were informed that any DVD returned by patients due to having non-Tysabri content would be collected from the clinic and returned for destruction.

A face-to-face meeting was held with the current agency on Monday, 20 June. In addition to quality control steps which were in place at the manufacturer, further agreed, specific and documented quality control steps had been put in place for all electronic media manufactured by the current agency for Biogen Idec.

Although this was an unfortunate event, Biogen Idec strongly believed that this matter was out of its control. Biogen Idec submitted that it had acted promptly, diligently and with due care and consideration regarding the matter. The Tysabri material was reviewed and certified in accordance with the Code prior to release for manufacture. It had liaised closely with the current agency and Leo in a pro-active manner in an effort to implement quality control steps which exceeded requirements specified in the Code regarding review and approval of promotional and non-promotional materials. Biogen Idec did not believe it was in breach of Clauses 22.1, 9.1 or 2. It had maintained high standards in relation to the prompt withdrawal of materials, communication to the sales teams and Leo following the first detection of the production error.

In response to a request from the case preparation manager for further information Biogen Idec confirmed that the items returned by the representative were a DVD and a DVD case. The DVD case in question was correctly identified with Biogen Idec and Tysabri branding. The artwork on the returned DVD itself also was identifiable with the Biogen Idec and Tysabri logo, identified by item number, date of preparation, entitled 'A guide to MS and how Tysabri works', and supplemented by the clear statement 'For use only by patients who have been prescribed TYSABRI. Provided as a service to medicine by Biogen Idec Ltd'. However, the content contained Xamiol material only. No Tysabri information was present.

The information Biogen Idec sent to the Authority was a direct copy of all of the electronic content available on the single affected DVD the company had in its possession. Copies of exactly the same disks were sent to Leo on 17 June. For Leo's reference only, Biogen Idec labelled the disk 'Xamiol Patient Material for Leo'.

The DVD and DVD case provided to the sales force were not mislabelled. The representative played the content on the DVD, noticed that the DVD played Xamiol material, and promptly notified Biogen Idec.

The DVD was played prior to final certification in 2008. The certification process at that time involved hard copy review of transcripts and visual material, followed by review of the electronic media. A certification sticker corresponding to the item number was applied to the DVD cover.

Copies were provided of the final certification relating to the original Tysabri DVD content (TY00-PAN-23515, August 2008) and the re-certification of

the DVD and addition of further safety information (TY-PAN-0177c, August 2010). The item returned by the representative was visually identified and corresponded to these certified items, with the exception that the content of the DVD did not correlate with the content of the certified item. It solely contained the Xamiol information which was provided to Leo on 17 June. In addition a copy of the final certification of the updated DVD case artwork and design (TY-PAN-0177d, August 2010) was also provided to the Authority. A copy of the Tysabri DVD in its correct form, as certified, was provided.

As previously stated, the error occurred post-certification, during product manufacture. Although Biogen Idec fully appreciated and understood the concerns expressed by Leo, it considered that it had made all practicable efforts to support the company over the past weeks.

In response to a request from the Panel for further information, Biogen Idec confirmed that the DVD content was examined prior to final certification on 20 August 2010, as stated on the certificate. Biogen Idec stated that it was not possible to retain a physical copy of the item with the electronic job bag, however the copy of the actual DVD provided by the previous agency for signatory review and certification was filed and retained by the affiliate. A copy was provided. This was not a production copy, therefore was unmarked and unbranded. Production copies of the DVD were manufactured post-certification and provided to the sales force from August 2010.

Biogen Idec clarified that the erroneous DVD in question did not relate to material produced by the previous agency following certification of the material. Material from the previous agency production run was provided post-certification to health professionals during 2010, and utilised for 'in house' training during this time. No errors were observed by Biogen Idec or reported from the field from the previous agency production run. The erroneous DVD in question related to the production run from the current agency during the first quarter of 2011, following transfer of Tysabri DVD manufacture from the previous to the current agency. There were no changes to content. The material was not examined again or re-certified, given that it had not changed. The item number remained the same.

Biogen Idec outlined that the quality control measures in place during the manufacturing period were as follows:

- ISO9001 quality standards were in place at the current agency and the sub-contracted manufacturer. Quality Control (QC) checks were implemented in accordance with internal production protocols. The identity of the operator responsible for the production process was recorded on the QC record (initials or signature of the checker and counter (double) checker were recorded).
- Human error relating to inadvertent uploading of Xamiol material onto the Tysabri production DVD was noted following an investigation by the current agency.

To further enhance quality and mitigate risk of inadvertent error, the following additional quality control steps were agreed and put in place on 20 June 2011 for reproduction/resupply of the DVD following a face-to-face meeting with the current agency:

a) The agency would take a screen grab of the names of folders on the final proof copy of the DVD, and check vs the same information provided by Biogen Idec's creative agency prior to manufacture.

b) Total file size would be checked vs material received from the creative agency.

c) Last date modified (date and time record) would be checked vs material received from the creative agency.

Details would be captured on a proof approval form, which would be sent (along with final proof) to Biogen Idec. Final proof content would be checked at Biogen Idec, and the signed form would be returned to the agency (copy of which would be uploaded onto the relevant job bag internally). Three copies from the full production run would also be sent to Biogen Idec for checking.

Following a request from the Panel for clarification of the comment made by the manufacturer that 'the error might not be universally apparent', Biogen Idec explained that it had been informed of one erroneous Tysabri DVD. During the course of the investigation, the current agency stated that the presence of Leo material on its DVD might not be apparent upon viewing for every DVD it produced due to difference between hardware operating systems. Biogen Idec acknowledged that it did not fully understand how this could be so. As stated previously, whether or not this was an isolated case could not be verified by the manufacturer, therefore Biogen Idec decided to destroy remaining stock from the production run (738 out of 1,015 DVDs) regardless of content, and recall remaining Tysabri DVDs held by its representatives and within clinics. Biogen Idec considered that taking prompt action based on the assumption that all DVDs from the current agency production run might have been affected was more appropriate than initiating an investigation to determine the number of DVDs affected and subsequently initiating a selective recall.

PANEL RULING

The Panel noted that Clause 22.1 prohibited the promotion of a prescription only medicine to the public. The Panel noted that promotional material for Leo's product Xamiol had been placed on a DVD provided to patients who had been prescribed

Tysabri. According to Biogen Idec this had occurred due to human error on a production run at a third party DVD manufacturer some months after the DVD was certified. The Panel did not accept Biogen Idec's submission that this matter was out of its control. It was a well established principle that a company was responsible for the acts or omissions of its agents or third parties. If this were not the case companies would be able to rely on such acts or omissions to circumvent the requirements of the Code. Biogen Idec was responsible for the acts or omissions of the DVD manufacturer.

The Panel noted that a DVD distributed to patients contained a video clip for a prescription only medicine. A prescription only medicine had thus been promoted to the public, and the Panel ruled a breach of Clause 22.1.

The Panel noted that Biogen Idec had certified the DVD in question on 20 August 2010 and copies were provided to the sales force for distribution after 24 August 2010. Biogen Idec had engaged a new company to manufacture the DVD in the first quarter of 2011. The Panel noted that the manufacturing process involved uploading the approved electronic file on to the DVD; a process which was open to human error. The Panel noted the risk of human error and the serious consequences if such risk materialized in relation to material directed at patients. The Panel considered it would have been good practice for Biogen Idec, prior to distribution, to have checked a DVD from the production run against that certified by the company. This was especially so given it was working with a new manufacturer.

The Panel was concerned that the error was discovered not by process checks at head office, but by a representative in the field. The Panel considered that the quality checks that Biogen Idec put in place as a result of this complaint should have been in place from the outset. These checks were particularly important when the material produced was intended for patients. High standards had not been maintained, and a breach of Clause 9.1 was ruled.

The Panel noted that the DVD in question appeared to have been certified in accordance with the Code. It was unfortunate that Biogen Idec had been let down by its DVD manufacturer. Nonetheless, a prescription only medicine had been advertised to the public. The Panel noted its comment above about the quality checks now in place at Biogen Idec. The Panel noted its rulings of breaches of the Code above and considered, on balance, that the circumstances did not warrant additional censure. A ruling of a breach of Clause 2 was a sign of particular censure, and was reserved for such circumstances. The Panel did not consider on balance that the circumstances brought discredit upon or reduced confidence in the industry, and ruled no breach of Clause 2.

Proceedings commenced	**27 June 2011**
Case completed	**4 August 2011**

CASE AUTH/2417/6/11

PRIMARY CARE TRUST HEAD OF MEDICINES MANAGEMENT v SERVIER

Promotion of Procoralan

A primary care trust (PCT) head of medicines management alleged that Servier had promoted Procoralan (ivabradine) for the unlicensed indication of heart failure. Procoralan was indicated for the symptomatic treatment of chronic stable angina.

Emails about the use of ivabradine in heart failure which had passed between the PCT and a medical liaison specialist (MLS) with Servier were provided. In one of the emails the MLS explained that he was not part of the sales force team and that his role was to deal with the non licensed indications for Procoralan. Details of the licensed indication for Procoralan were given as well as information about Servier's application for an extension for heart failure. The MLS stated in his email that he had seen many local consultant cardiologists and the responses had been very positive. 'In some areas clinicians are already using the product (off licence) in heart failure. As a consequence I felt it appropriate to make contact, to ensure that ... you would have an opportunity to be brought up to date with the most recent data ...'. This email ended with an invitation to meet to discuss heart failure, ivabradine and the patient pathway. The recipient replied by copying in the medicines management lead pharmacist. The MLS replied and suggested a joint meeting to which he would 'bring some data and modelling tools'. The medicines management lead noted that Procoralan had to be licensed for heart failure before it could be funded and that the contraindications and cautions in the summary of product characteristics (SPC) referred to heart failure and that GPs could not be expected to prescribe a contraindicated therapy. A number of steps were set out that needed to be taken before the matter could be discussed. In the final email the MLS referred to the licensed status of Procoralan and noted there was a lot of published data in respect of heart failure but he had never suggested it be prescribed for heart failure at the moment. He wanted to bring everyone up to speed, to look at existing pathways and to report on the thinking of consultants in cardiology/care of the elderly.

The detailed response from Servier is given below.

The Panel noted the licensed indications for Procoralan. It also noted that the special warnings and precautions for use section of the SPC stated, under headings of 'Special warnings' and 'Chronic heart failure' that heart failure must be appropriately controlled before ivabradine treatment was considered. Ivabradine was contraindicated in moderate to severe heart failure and should be used with caution in patients with mild heart failure.

The Panel noted that Servier expected to gain a chronic heart failure indication for Procoralan towards the end of 2011.

The Panel noted that the Code defined 'promotion' as 'any activity undertaken by a pharmaceutical company or with its authority which promotes the prescription, supply, sale or administration of its medicines'. This was followed by a list of activities within that definition and a number that were not. There was an exemption to the definition of promotion for 'replies made in response to individual enquiries from members of the health professions or appropriate administrative staff'. This exemption related to unsolicited enquiries only and allowed pharmaceutical companies to answer specific questions from health professionals and appropriate administrative staff. Questions about unauthorized medicines or unauthorized indications frequently came up in this context. To ensure that the exemption was only used in relation to genuine enquiries the word 'unsolicited' was used. This was to clearly separate the promotion of medicines from the role of medical information departments.

The Code defined a representative as a representative calling on members of the health professions and administrative staff in relation to the promotion of medicines.

The supplementary information to the Code stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion. In this regard the context in which the exchange took place and the audience would be important factors in determining whether the activity was acceptable under the Code. The proactive provision of information about the unauthorized use of a medicine was very likely to be seen as promotion.

The supplementary information to Clause 3.1, Advance Notification of New Products or Product Changes, referred to various NHS organisations

and their need to establish their likely budgets two to three years in advance in order to meet Treasury requirements and for them thus to receive advance information about the introduction of new medicines, or changes to existing medicines, which might significantly affect their future level of expenditure. It was noted that when this information was required, the medicines concerned would not be the subject of marketing authorizations (though applications would often have been made) and it would thus be contrary to the Code for them to be promoted. The supplementary information included the requirement that advance notification must include the likely cost and budgetary implications which must make significant differences to the likely expenditure of health authorities etc.

The Panel noted that there were two issues to be considered, firstly whether the MLS who had written the emails had acted in accordance with the Code and secondly whether the company's materials and instructions were in accordance with the Code.

Servier provided a copy of what it described as an access letter for the MLS team to use to contact budget holders in the NHS about Procoralan which stated that Servier would shortly apply to extend the current licensed indication and if successful a new indication for chronic heart failure would be expected towards the end of 2011. The letter detailed the current indication and referred to the recipient as someone who had a role in policy making or deciding budgets for cardiovascular disease within the NHS. The letter also stated that the Code advised that advance budgetary information might be provided to policy influencers and those responsible for budgetary decisions to aid in future planning. The company wished to provide the relevant clinical and budgetary data relating to the product to assist the planning process and that the recipient would be contacted by the MLS to arrange a meeting. The date of preparation of the access letter was August 2010. The approval form for the letter described it as a 'budget impact letter'.

The Panel noted that advanced information could only be supplied if the product had a significant budgetary implication. The Panel queried whether the introduction of Procoralan for chronic heart failure would have a significant budgetary implication. The access letter did not refer to the budgetary implication. In the Panel's view if this condition was not met then advanced notification was not permitted under the Code.

It appeared to the Panel that Servier might have carried out an advance notification process for the unlicensed indication since at least August/September 2010. However if the licence was expected by the end of 2011 the timeframe appeared to be inconsistent with that stated in the relevant supplementary information as being 2 – 3 years before launch. The Panel queried whether the information had been supplied early enough such that budget holders etc could be reasonably expected to act upon it.

The MLS job description set out the main purpose of the job which was to: provide field-based medical information services; respond to medical enquiries; manage non interventional studies and deliver medical and educational goods and services and support the cardiovascular key account managers including provision of relevant clinical and scientific training. The principal responsibilities in the job description included the above and in addition the non-promotional exchange of medical and scientific information. This was described as supporting the legitimate exchange of scientific and medical information with cardiovascular health professionals through advisory boards and 1:1 visits. This would include advance notification of new products or product changes as set out in the Code.

The Panel noted that the MLS job description had amalgamated a number of key activities each of which was subject to different requirements in the Code. This was not helpful and in the Panel's view could lead to confusion as to the precise nature of any activities undertaken. The Panel noted that it had previously been decided that it was not necessarily unacceptable to have employees focussing on the provision of information prior to the grant of the marketing authorization or prior to the licensing of an indication. The arrangements and activities of such employees had to comply with the Code and they should be comprehensively briefed about the Code. Companies needed to ensure that in this difficult area the arrangements and activities were very carefully controlled and managed. The importance of documentation and instruction could not be overestimated.

The Panel noted that the MLS team was provided with three presentations, for use 'on request of medical enquiries': 'Ivabradine in Heart Failure', 'Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial' and 'SHIFT-PRO: Patient Reported Outcomes Quality of Life SubStudy'. The second slide of each presentation detailed the licensed indication for Procoralan. This was followed by the statement that the use of ivabradine outside this indication was unlicensed and could not be recommended. A statement that heart failure must be appropriately controlled before considering ivabradine treatment was followed by details of the contraindication and caution in the Procoralan SPC. The second presentation stated that the contraindication in moderate to severe heart failure was due to lack of data. This reason was not included in the SPC. The

presentations had been certified, the first presentation as promotional material and the other two as non-promotional material.

The MLS team was also given advanced budgetary notification material and training on the calls. Two consecutive slides detailed the supplementary information to the Code which provided the basis on which advanced notification could be given. Some of these were highlighted in bold underlined type but not the need for the likely cost and budgetary implications to be indicated and to be significant. The MLS team was also provided with a cost effectiveness analysis presentation for use of ivabradine in heart failure in the UK based on the SHIFT trial results. Although the contraindication for moderate to severe heart failure was included in slide 2, the caution in the SPC regarding mild heart failure was not. The presentation gave information about the cost per QALY (quality adjusted life year). According to the certificate the presentation had been approved for use following an unsolicited request from a health professional about the cost effectiveness of Procoralan in heart failure. The MLS team was also provided with a budget impact model for ivabradine in heart failure based on the SHIFT trial which had been approved for use in response to an unsolicited request for information on the cost effectiveness of Procoralan in heart failure. The Panel queried whether these materials constituted the 'data and modelling tools' which the MLS in question had proactively offered.

General guidance on responding to enquiries about heart failure was provided to key account managers and MLS staff. In responding to questions about the SHIFT study key account managers were instructed to generally include mention of the ivabradine licensed indication and that following the results the company planned to apply for a heart failure licence. Key account managers were then instructed to say that they could not discuss this further but should further information be required the preferred option for follow up was for a cardiovascular MLS to arrange a meeting.

In relation to the company's materials and instructions the Panel was extremely concerned about the activities with regard to the advanced notification of the use of Procoralan in heart failure. The Panel considered that on the evidence before it the MLS activity in this regard did not meet the conditions set out in the Code in relation to the need to demonstrate a significant budgetary implication and supply information about it. Servier's response did not show that the use of Procoralan in heart failure had a significant budgetary impact and no details had been provided in the access letter about the likely cost and budgetary implication as required in the relevant supplementary information.

The Panel did not consider that the MLS's role was non-promotional. Servier had not limited the activities to responding to unsolicited requests. The company had arranged for its staff to proactively call upon health professionals and others to raise awareness of the use of Procoralan for an unlicensed indication. In that regard the Panel noted that in the last 6 months, the MLS in question had contacted 57 health professionals/budget holders about the use of ivabradine in heart failure. The company's activity amounted to the promotion of Procoralan for an unlicensed indication, heart failure, which was the subject of a contraindication or caution in the SPC. A breach of the Code was ruled. The Panel considered that high standards had not been maintained. A breach of the Code was ruled. Given its ruling that the MLS role was promotional, the failure to comply with the relevant requirements of the Code was ruled in breach of the Code.

The Panel noted that Clause 2 of the Code was a sign of particular censure and reserved for such. The Panel considered that the activity at issue amounted to a softening of the market for using Procoralan in heart failure, a condition which was the subject of a contraindication or caution in the SPC. This brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

In relation to the emails provided by the complainant the Panel considered that the MLS in question had promoted Procoralan for an unlicensed indication. In this regard it noted that the MLS had seen many consultant cardiologists whose responses had been positive and that some were already using the product off licence in heart failure. A breach of the Code was ruled. The emails did not mention that the product was contraindicated or the subject of an SPC caution in certain types of heart failure. This potentially had a negative impact on patient safety. High standards had not been maintained and a breach of the Code was ruled. [This was the only breach ruling accepted by Servier – all of the others were appealed]. The Panel noted its ruling of a breach of Clause 2 in relation to the company's activities and decided in the circumstances that the conduct of the MLS in question did not warrant a separate ruling in relation to Clause 2.

The Panel considered that overall Servier's actions were unacceptable; given that no budgetary impact for ivabradine in heart failure was stated, the MLS's activities did not constitute advance notification of a new indication. Overall the Panel considered that Servier's activity amounted to the promotion of ivabradine for an unlicensed indication. The Panel decided to report the company to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

Upon appeal by Servier the Appeal Board noted

that the promotion of a medicine prior to the grant of its marketing authorization was prohibited and that promotion of a medicine must be in accordance with the terms of its marketing authorization and not inconsistent with its SPC. The supplementary information to the Code set out guidance in relation to certain situations including the provision of advanced notification of new products or product changes. This supplementary information included a requirement that such information must include the likely cost and budgetary implications and this must be such as to make a significant difference to the likely expenditure of health authorities, trusts and the like.

The Appeal Board noted that the emails at issue sent by the MLS did not discuss the anticipated cost or the budgetary implications of using Procoralan for heart failure. The Appeal Board noted that one of the MLS's emails stated that 'I have seen many consultant cardiologists in the [local] region and the responses have been very positive. In some areas clinicians are already using the product (off licence) in heart failure. As a consequence I felt it appropriate to make contact, to ensure that ... you would have an opportunity to be brought up to date with the most recent data that we have.' The Appeal Board considered that the very positive description of the heart failure indication in the absence of any discussion either of the budgetary implications or the significance of the difference in expenditure meant that the MLS had promoted Procoralan for an unlicensed indication. The email in question could not take the benefit of the exemption for advance notification set out in the supplementary information to the Code. The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted that 'representative' was defined in the Code as 'a representative calling on members of the health professions and administrative staff in relation to the promotion of medicines.' It considered that its ruling that the product had been promoted for an unlicensed indication did not mean that it considered that the MLS job description described a representative's role as defined in the Code. The Appeal Board thus ruled no breach of the Code as the clause at issue applied to the conduct of representatives. The appeal on this point was successful.

The Appeal Board noted that advanced information about an unlicensed indication could only be supplied if such use of the product had a significant budgetary implication and the information included details of the likely cost and budgetary implication. The relevant supplementary information to the Code set out detailed conditions. The Appeal Board noted Servier's submission for the appeal that its Budget Impact Model, based on the results of the SHIFT study (Swedburg *et al*), showed a typical net annual cost of treating heart failure with Procoralan of £3,000-£9,000 per 100,000 head of population. The Appeal Board noted in the email correspondence the head of prescribing and medicines management stated that the estimated cost to the PCT of using Procoralan in a suitable population was around £75,000/year but there would be 'therapeutic creep' and so the cost would be considerably more. The head of prescribing and medicines management also stated that the patients in the study were not on optimum doses of beta-blocker. The Appeal Board considered that NHS managers were likely to regard such potential increases in budgetary requirements as significant particularly given the current economic environment. The Appeal Board considered that the licence extension application for Procoralan for heart failure satisfied the condition in the supplementary information to the Code that advanced notification information might be provided for '... a product which is to have a significant addition to the existing range of authorized indications ...'.

The Appeal Board did not consider that starting the advanced notification in August/September 2010 for changes to the licence expected by the end of 2011 was unacceptable. The Appeal Board noted Servier's submission for the appeal that the licence was now expected in April/June 2012. The Appeal Board noted the access letter discussed the ivabradine licence application to add an indication for chronic heart failure. The letter detailed the current licensed indication and stated that the Code advised that advanced budgetary information might be provided to policy influencers and those responsible for budgetary decisions to aid future planning. The Appeal Board considered that the purpose of the letter was to determine if recipients were responsible for budgetary decisions and if so to provide '... the relevant clinical and budgetary data relating to this product to assist your planning process'. The letter also stated that the author intended to contact the recipient to organise a meeting.

The Appeal Board considered that advanced notification was a difficult area and care was needed to satisfy the relevant requirements of the supplementary information to the Code. The Appeal Board was concerned about some of the claims made in material used by the MLSs and also about their proactive contact of key opinion leaders. Nonetheless the Appeal Board did not consider that the company's activity amounted to the promotion of Procoralan for an unlicensed indication. The Appeal Board also noted that the complainant had emphasised the role of the individual MLS as evidenced by the email trail rather than activities undertaken by the company. The Appeal Board ruled no breach of the Code. The appeal on this point was successful.

The Appeal Board noted the rulings of a breach of the Code in relation to the MLS in question. The Appeal Board considered that Servier should have more closely controlled its MLS team. High standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

During its consideration of this point the Appeal Board noted Servier's recent decision that emails sent by the MLS team be copied to their manager but queried whether this on its own introduced sufficient control.

The Appeal Board noted its rulings above and considered that a ruling of a breach of Clause 2 was not warranted and so no breach of that clause was ruled. The appeal on this point was successful.

Given its rulings the Appeal Board decided to take no further action in relation to the report from the Panel.

A primary care trust (PCT) head of medicines management alleged that Servier had promoted Procoralan (ivabradine) for the unlicensed indication of heart failure. Procoralan was otherwise indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm, in adults unable to tolerate or with a contraindication to the use of beta-blockers or in combination with beta-blockers in patients inadequately controlled with an optimal beta blocker dose and whose heart rate was greater than 60 beats per minute.

COMPLAINT

The complaint was prompted by emails about the use of ivabradine in heart failure which had passed between the PCT and a medical liaison specialist (MLS), cardiovascular. Copies were provided.

The email trail started with emails from the MLS to the chief executive at a community interest company (CIC) in relation to a presentation by the chief executive at a meeting organised by the MLS. The second email asked for contact details so that the MLS could contact someone in CIC to discuss heart failure pathways and possible heart failure audits. The chief executive suggested the director of clinical transformation who was in the process of being appointed. The MLS contacted the director of clinical transformation in June explaining that he was not part of the sales force team and that his role was to deal with the non licensed indications for Procoralan. He referred to his previous role in the NHS. Details of the licensed indication were given as well as information about Servier's application for an extension for heart failure which was expected by the end of 2011 or early 2012. The MLS stated in his email that he had seen many consultant cardiologists in the region and the responses had been very positive. 'In some areas clinicians are already using the product (off licence) in heart failure. As a consequence I felt it appropriate to make contact, to ensure that as the director of clinical transformation, you would have an opportunity to be brought up to date with the most recent data …'. This email ended with an invitation to meet to discuss heart failure, ivabradine and the patient pathway. The recipient replied by copying in the medicines management lead pharmacist. The MLS replied and suggested a joint meeting to which he would 'bring some data and modelling tools'. The medicines management lead noted that in order to assure funding for ivabradine in heart failure the product needed to be licensed for the indication and that the promotion of an unlicensed indication was prohibited. The contraindications and cautions in the Procoralan summary of product characteristics (SPC) in relation to use in heart failure were mentioned and that GPs could not be expected to prescribe a contraindicated therapy. A number of steps were set out that needed to be taken before the matter could be discussed. These included a review of evidence and cost effectiveness, whether the PCT would fund it, the estimated cost was £75,000 per year and there would be additional 'therapeutic creep' costs. Finally a recent study had noted that patients were not on the optimum doses of beta blocker which was current practice. In the final email the MLS referred to the licensed status of Procoralan and noted there was a lot of published data in respect of heart failure but he had never suggested it be prescribed for heart failure at the moment. His intention was to bring everyone up to speed, to look at existing pathways and to report on the thinking of consultants in cardiology/care of the elderly. The plan was to look at economic models and quality of life issues and how these impacted on present management pathways.

When writing to Servier, the Authority asked it to respond in relation to Clauses 2, 3.2, 9.1 and 15.2 of the Code.

RESPONSE

Servier regretted that this complaint had arisen. It was nonetheless grateful to both the complainant and the PMCPA for bringing the email thread to its attention. This communication was unclear and ambiguous, and hence did not meet Servier or industry standards. However, following investigation, Servier believed that the specific allegation was unfounded. Servier sought to reassure the PMCPA in this regard.

Servier attached great importance to meeting its obligations with regard to the Code and relevant regulations. It invested significantly in appropriate staff, procedures and training to ensure that this occurred. These approaches were reflected in the company organogram, standard operating procedures (SOPs), job descriptions and other documentation supplied as requested for the scrutiny and reassurance of the PMCPA.

Pre-licence communication

Pre-licence communication was allowed by Servier's procedures only in tightly-limited circumstances. These activities were always carried out by appropriately-trained, non-promotional staff within the medical affairs team. Where these staff were field-based Servier referred to them as MLS. Servier noted that this was not a 'representative' role as defined in Clause 1.6. Servier allowed pre-licence communication when it was:

– in response to unsolicited medical enquiries
– advanced budgetary notification to policy makers/budget holders, and
– the legitimate exchange of medical and scientific information (for example briefing an opinion leader for a presentation to an advisory board).

MLS responsibilities also extended to liaison related to research – both investigator-led and non-interventional studies.

The MLS at issue was a senior and respected member of the Servier MLS team and had never worked in a promotional role. His previous NHS background, together with his training records, demonstrated his suitability and preparedness for the MLS role. The MLS's immediate manager carried out field visits with him on a regular two-monthly basis. In his role as an MLS, and indeed in his career to date, his ethics and integrity had never been questioned.

The MLS covered a large area. In the last six months he had made 132 contacts (all types, including research liaison as described above) of which 69 were specifically related to ivabradine and heart failure. The heart failure-related contacts were spread across 100 organisations, covering 57 individual health professionals/budget holders.

The email thread

Clause 9.1

Servier submitted that its investigation had shown that, as might be predicted from his role and the setting, the intent of the MLS in question was to identify the relevant policy and budget holders in the new consortium structure and to engage with them regarding future planning under the advanced notification provision. Indeed the first contact was a follow-up email to a speaker from an advisory board who was chief executive of an emerging primary care consortium. Subsequent mails were the result of onward referral to a policy maker for heart failure within the new consortium and by him to the appropriate budget holder. Servier accepted this explanation as evidence that the intent of the communication was advanced notification.

However, Servier also noted that the single email thread was unclear, ambiguous and included extraneous references. In advising Servier of the complaint, the Authority had noted the use of the phrases 'bringing everyone up to speed … and report on what consultants in cardiologists/care of the elderly were thinking' and 'heart failure audits'. Servier additionally noted 'I have seen many consultant cardiologists in the [local] region and the responses have been very positive. In some areas clinicians are already using the product (off licence) in heart failure' as meriting investigation/clarification. As stated above Servier was now satisfied as to the true intent of the contacts. Servier also noted that when specifically questioned, the MLS stated that the references to clinician feedback/existing prescribing were important context for this discussion (being predictive of likely local uptake post-licence). Nevertheless both the MLS and his immediate manager accepted and understood that communication should have been clearer and more explicit in its intention. It hence fell below the standard of communication expected by Servier. In relation to Clause 9.1, Servier acknowledged that the ambiguity appeared to have resulted in misperception of the MLS's intent (as promotional) by at least one recipient. Servier hence accepted that high standards had not been maintained at all times.

Clause 3.2

Servier took this complaint extremely seriously and did not seek to minimise its importance. It highlighted that even with robust procedures, isolated anomalies might sometimes occur. However for a complaint of pre-licence promotion to be upheld Servier believed that it would be necessary to demonstrate, on the balance of probabilities, that promotion (defined in the Code as promotion of prescription, supply, sale or administration of ivabradine for heart failure) had occurred. In this regard Servier noted that the pre-licence context, the non-promotional role of the MLS in question and a sense of future planning were consistent in the communication in the thread. It was equally clear in Servier's view that engagement with these health professionals was in their roles as policy maker and budget holder at CIC respectively, and not in relation to any potential role in the prescribing or dispensing of ivabradine. Indeed the MLS in question was referred on to each contact by the precedent, commencing with the chief executive. Equally from the recipient's perspective it should be readily understood that the MLS in question was not a sales representative; this point was explicitly made in the first contact and forwarded with all subsequent communication. Lastly Servier noted that the email title 'Re: Ivabradine in heart failure' was added by one of the recipients during the correspondence, it was not written by the MLS.

Overall, Servier believed that neither the nature, purpose, nor consequence of these contacts was promotional. As a result Servier did not believe that Clause 3.2 had been breached.

Clauses 15.2 and 2

In relation to Clause 15.2 Servier observed that whilst the issue concerned communication by a Servier employee, this employee was not a 'representative' as defined by the Code. Further, following investigation Servier believed the complainant's allegation of pre-licence promotion was unfounded. Servier standards and therefore Clause 9.1 were breached in an isolated circumstance and this was regrettable. Servier did not believe however that this risked the reputation of the industry.

Actions taken by Servier

Notwithstanding his integrity and professional record the MLS in question was suspended for seven working days during the investigation of this complaint. Following the investigation, which satisfied Servier as to his intent, he had been deployed on a head office project at least until such time as Servier had completed implementation of new processes outlined below, team re-training on these, and team retraining on advanced notification and the Code.

Acknowledging a breach of Clause 9.1, Servier was acting to prevent a recurrence through new processes. These required that all emails from an MLS to a health professional (including those in commissioning groups) were copied to the national MLS manager in order to support standardised communication and compliance. The company would also require that once an appropriate policy maker or budget holder was identified, the certified advanced notification letter be used.

Additionally, the PMCPA's conclusions would be reflected in a presentation to all MLS staff regarding the context and outcomes of this complaint together with a reminder of updated Servier policy regarding pre-licence communication. A summary of the content and outcome of this complaint would also be communicated to all commercial Servier staff.

PANEL RULING

The Panel noted the licensed indications for Procoralan. It also noted that the special warnings and precautions for use section of the SPC stated, under headings of 'Special warnings' and 'Chronic heart failure' that heart failure must be appropriately controlled before ivabradine treatment was considered. Ivabradine was contraindicated in heart failure patients with NYHA functional classification III-IV and should be used with caution in heart failure patients with NYHA functional classification I-II.

The Panel noted that Servier expected to gain a chronic heart failure indication for Procoralan towards the end of 2011.

The Panel noted that Clause 1.2 of the Code defined 'promotion' as 'any activity undertaken by a pharmaceutical company or with its authority which promotes the prescription, supply, sale or administration of its medicines'. This was followed by a list of activities within that definition and a number that were not. There was an exemption to the definition of promotion for 'replies made in response to individual enquiries from members of the health professions or appropriate administrative staff or in response to specific communications from them whether of enquiry or comment, including letters published in professional journals, but only if they relate solely to the subject matter of the letter or enquiry, are accurate and do not mislead and are not promotional in nature'. Further guidance was given in the supplementary information to Clause 1.2, Replies Intended for Use in Response to Individual Enquiries, which stated:

'The exemption for replies made in response to individual enquiries from members of the health professions or appropriate administrative staff relates to unsolicited enquiries only. An unsolicited enquiry is one without any prompting from the company. In answering an unsolicited enquiry a company can offer to provide further information. If the enquirer subsequently requests additional information this can be provided and would be exempt from the Code provided the additional information met the requirements of the exemption. A solicited enquiry would be one where a company invites a person to make a request. For example, material offering further information to readers would be soliciting a request for that information. Placing documents on exhibition stands amounts to an invitation to take them. Neither can take the benefit of this exemption.'

The reason for the exemption was to allow pharmaceutical companies to answer specific questions from health professionals and appropriate administrative staff. Questions about unauthorized medicines or unauthorized indications frequently came up in this context. To ensure that the exemption was only used in relation to genuine enquiries the word 'unsolicited' was used. This was to clearly separate the promotion of medicines from the role of medical information departments.

Clause 1.6 of the Code defined a representative as a representative calling on members of the health professions and administrative staff in relation to the promotion of medicines.

The supplementary information to Clause 3 stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion which was prohibited under that or any other clause. In this regard the context in which the exchange took place and the audience would be important factors in determining whether the activity was acceptable under the Code. The proactive provision of information by a pharmaceutical company about the unauthorized

use of a medicine was very likely to be seen as promotion.

The supplementary information to Clause 3.1, Advance Notification of New Products or Product Changes, stated that health authorities and health boards and their equivalents, trust hospitals and primary care trusts and groups needed to establish their likely budgets two to three years in advance in order to meet Treasury requirements and there was a need for them to receive advance information about the introduction of new medicines, or changes to existing medicines, which might significantly affect their level of expenditure during future years. It was noted that when this information was required, the medicines concerned would not be the subject of marketing authorizations (though applications would often have been made) and it would thus be contrary to the Code for them to be promoted. The supplementary information gave guidance on the basis on which such advance information could be provided including the requirement to include the likely cost and budgetary implications which must make significant differences to the likely expenditure of health authorities etc.

The Panel noted that there were two issues to be considered, firstly whether the MLS who had written the emails had acted in accordance with the Code and secondly whether the company's materials and instructions were in accordance with the Code.

Servier provided a copy of what it described as an access letter for the MLS team to use to contact budget holders in the NHS. This was headed 'Advance Budget Notification of an Application to Extend the Licensed Indication of Ivabradine' and stated that Servier would shortly apply to extend the current licensed indication for ivabradine and if successful a new indication for chronic heart failure would be expected towards the end of 2011. The letter detailed the current indication and referred to the recipient as someone who had a role in policy making or deciding budgets for cardiovascular disease within the NHS. The letter also stated that the ABPI Code advised that advance budgetary information might be provided to policy influencers and those responsible for budgetary decisions to aid in future planning. The company wished to provide the relevant clinical and budgetary data relating to the product to assist the planning process and the recipient would be contacted by the MLS to arrange a meeting. The date of preparation of the access letter was August 2010. The approval form for the letter described it as a 'budget impact letter'.

The Panel noted that advanced information could only be supplied if the product had a significant budgetary implication. The Panel queried whether the introduction of Procoralan for chronic heart failure would have a significant budgetary implication. There was no mention in the access letter of whether or not there was a significant budgetary implication. In the Panel's view if this condition was not met then advanced notification was not permitted under the Code.

It appeared to the Panel that Servier might have carried out an advance notification process for the unlicensed indication since at least August/September 2010. However if the licence was expected by the end of 2011 the timeframe appeared to be inconsistent with that stated in the relevant supplementary information as being 2 – 3 years before launch. In that regard, the Panel queried whether the information had been supplied early enough such that budget holders etc could be reasonably expected to act upon it.

The MLS (cardiovascular) job description set out the main purpose of the job which was to:

- provide field-based medical information services
- respond to medical enquiries
- manage non interventional studies and deliver medical and educational goods and services
- support the cardiovascular key account managers including provision of relevant clinical and scientific training.

The principal responsibilities in the job description included the above and in addition the non-promotional exchange of medical and scientific information. This was described as supporting the legitimate exchange of scientific and medical information with health professionals in the field of cardiovascular medicine through the organisation of advisory boards as well as 1:1 visits. This would include advance notification of new products or product changes as set out in Clause 3 of the Code.

The Panel noted that the MLS job description had amalgamated a number of key activities each of which was subject to different requirements in the Code. This was not helpful and in the Panel's view could lead to confusion as to the precise nature of any activities undertaken. The Panel noted that it had previously been decided that it was not necessarily unacceptable for companies to have employees focussing on the provision of information prior to the grant of the marketing authorization or prior to the licensing of an indication. The arrangements and activities of such employees had to comply with the Code. Such employees should be comprehensively briefed about the Code. The area was difficult and companies needed to ensure that the arrangements and activities were very carefully controlled and managed. The importance of documentation and instruction could not be overestimated.

The Panel noted that the MLS team was provided with three presentations, for use 'on request of medical enquiries': 'Ivabradine in Heart Failure', 'Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial' and 'SHIFT-PRO: Patient Reported Outcomes Quality of Life SubStudy'. The second slide of each

presentation detailed the licensed indication for Procoralan. This was followed by the statement that the use of ivabradine outside this indication was unlicensed and could not be recommended. A statement that heart failure must be appropriately controlled before considering ivabradine treatment was followed by details of the contraindication and caution in the Procoralan SPC. The second presentation stated that the contraindication in NYHA functional classification III-IV was due to lack of data. This reason was not included in the SPC. The presentations had been certified, the first presentation as promotional material and the other two as non-promotional material.

The MLS team was also provided with advanced budgetary notification material including training on the calls. Two consecutive slides detailed the supplementary information to Clause 3.1 which provided the basis on which advanced notification of new products or product changes could be given. Some of these were highlighted by the use of bold underlined type. The need for the likely cost and budgetary implications to be indicated and to be significant was not highlighted in this way. The MLS team was also provided with a cost effectiveness analysis presentation for use of ivabradine in heart failure in the UK based on the SHIFT trial results. Although the contraindication for NYHA III-IV was included in slide 2, the caution in the SPC regarding NYHA I-II was not. The presentation gave information about the cost per QALY (quality adjusted life year). According to the certificate the presentation had been approved for use following an unsolicited request from a health professional regarding the cost effectiveness of Procoralan in heart failure. The MLS team was also provided with a budget impact model for ivabradine in heart failure based on the SHIFT trial. Again this had been approved for use in response to an unsolicited request for information on the cost effectiveness of Procoralan in heart failure. The Panel queried whether these materials constituted the 'data and modelling tools' which the MLS in question had proactively offered.

General guidance on responding to enquiries about heart failure were provided to key account managers and MLS staff. In responding to questions about the SHIFT study key account managers were instructed to generally include mention of the ivabradine licensed indication and that following the results the company planned to submit to the European Medicines Agency (EMA) for a licence in heart failure. Key account managers were then instructed to say that they could not discuss this further but should further information be required the preferred option for follow up was for a cardiovascular MLS to arrange a meeting.

In relation to the company's materials and instructions the Panel was extremely concerned about the activities with regard to the advanced notification of the use of Procoralan in heart failure. The Panel considered that on the evidence before it the MLS activity in relation to advanced notification did not meet the conditions set out in the supplementary information in relation to the need to demonstrate a significant budgetary implication and supply information about it. The response from Servier did not show that the use of Procoralan in heart failure had a significant budgetary impact and no details had been provided in the access letter about the likely cost and budgetary implication as required by point iv of the relevant supplementary information.

The Panel did not consider that the MLS's role was non-promotional. Servier had not limited the activities to responding to unsolicited requests. The company had arranged for its staff to proactively call upon health professionals and others to raise awareness of the use of Procoralan for an unlicensed indication. In that regard the Panel noted that in the last 6 months, the MLS in question had contacted 57 health professionals/budget holders about the use of ivabradine in heart failure. The company's activity amounted to the promotion of Procoralan for an unlicensed indication, heart failure, which was the subject of a contraindication or caution in the SPC. A breach of Clause 3.2 was ruled. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. Given its ruling that the MLS role was promotional, the failure to comply with the relevant requirements of the Code was ruled in breach of Clause 15.2.

The Panel noted that Clause 2 of the Code was a sign of particular censure and reserved for such circumstances. The supplementary information to that clause listed examples of activities likely to be in breach of Clause 2 including promotion prior to the grant of a marketing authorization and activities likely to prejudice patient safety. The Panel considered that the activity amounted to a softening of the market for using Procoralan in heart failure, a condition which was the subject of a contraindication or caution in the SPC. This brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

In relation to the emails provided by the complainant the Panel considered that the MLS in question had promoted Procoralan for an unlicensed indication. In this regard it noted phrases that the MLS had seen many consultant cardiologists whose responses had been positive and that some were already using the product off licence in heart failure. A breach of Clause 3.2 was ruled. The emails did not mention that the product was contraindicated or the subject of an SPC caution in certain types of heart failure. This potentially had a negative impact on patient safety. High standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel noted its ruling of a breach of Clause 2 in relation to the company's activities and decided in the circumstances that the conduct of the MLS did not warrant a separate ruling in relation to Clause 2.

The Panel considered that overall Servier's actions were unacceptable; given that no budgetary impact for ivabradine in heart failure was stated, the MLS's activities did not constitute advance notification of a new indication. Overall the Panel considered that Servier's activity amounted to the promotion of ivabradine for an unlicensed indication. The Panel decided to report the company to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BY SERVIER

Servier appealed the Panel's rulings of breaches of Clauses 2, 3.2, 9.1 and 15.2 in relation to the activities of the company and Clause 3.2 in relation to the activities of the MLS in question.

Servier acknowledged that, regrettably, its usual high standards were not maintained by the MLS concerned and so it had accepted the Panel's ruling of breach of Clause 9.1 in relation to his conduct. However, Servier denied that the email correspondence at issue amounted to unlicensed promotion and therefore appealed the ruling of a breach of Clause 3.2 in relation to the individual MLS. Servier was confident of its policies, procedures and MLS team to know that this was not the purpose of the communication, and should not have been interpreted as such. Servier fully stood by the important role played by its MLSs as testified by its commitment to further strengthen its policies and procedures relating to the team. However, the Panel had apparently assumed that this single, unfortunate incident reflected serious flaws in Servier's policies and company organisation. This called into question the proportionality and the evidence basis for the ruling. Servier therefore found itself having to defend fundamental aspects of its policies and company structure with regard to its MLS team, notwithstanding that this case concerned an isolated (albeit regrettable) incident.

Servier submitted that insufficient information was provided to enable it to understand how the Panel reached its conclusions. Indeed, the Panel summarised certain aspects of Servier's material and instructions and raised certain queries, before making the extremely serious allegation that 'The company's activity amounted to the promotion of Procoralan for an unlicensed indication …'. Servier did not accept this conclusion, and did not agree that it was justified on the basis of the evidence before the Panel, or at all. It was essential for Servier to obtain clarification on what exactly the Panel had criticised and why; the uncertainty affected the everyday operations of the MLS team and reduced morale.

Servier did not have a policy or practice of promoting Procoralan (or any other product) for an unlicensed indication. Pharmaceutical companies commonly maintained a field-based medical and scientific liaison team (ie the MLS role within Servier). In Servier's experience, such a team brought significant benefit to NHS health professionals and thus to public health. There was real value in having a field-based team of individuals with strong scientific backgrounds and a high degree of knowledge in the products and disease area at stake.

Servier thus queried the evidentiary basis and reasoning for the Panel's ruling that its activities breached Clauses 2, 3.2, 9.1 and 15.2 of the Code. These rulings appeared to be disproportionate and compromised legal certainty to the detriment of Servier's operation.

Servier submitted that the purpose of the MLS cardiovascular team was to address spontaneous enquiries about Procoralan which was why 'Answer medical enquiries' was listed as one of the principal responsibilities in the relevant job description. Procoralan was already licensed and marketed for angina, hence Servier received enquiries about a number of different aspects of the product, including safety, use by the elderly, use in heart failure, arrhythmias or acute coronary syndrome. Depending on the specific enquiry therefore, both on- and off-licence topics might be covered.

In developing the MLS role, Servier submitted that it had relied on the relevant sections of the Code concerning the provision/exchange of non-promotional scientific information, as well as previous rulings. Indeed, the Code made specific provision for factual responses to unsolicited enquiries (supplementary information to Clause 1.2), the legitimate exchange of medical and scientific information (supplementary information to Clause 3), advanced budgetary notification (supplementary information to Clause 3.1) and the maintenance of a scientific service (Clause 21). Against this background, Servier had relied on the Panel's ruling in Case AUTH/1910/11/06 that it was 'not necessarily unacceptable for companies to have employees focussing on the provision of information prior to the grant of the marketing authorization', provided that the arrangements and activities were carefully controlled and managed. Indeed, this decision was duly noted in one of the MLS training presentations approved by Servier ('ABPI Code Update: Focus on Field Based Medical Information – August 2008').

Further, the MLS role was developed in line with the practices of the industry as a whole: companies commonly maintained a field-based medical and scientific liaison team, a role which had evolved considerably in recent years. Indeed, the first Medical Science Liaison (MSL) conference to be held in the UK took place in 2010 ('The European MSL and Medical/Scientific Advisor Best Practices Conference', run by ExL Pharma). Servier provided a selection of the speaker presentations and noted that, compared with some pharmaceutical companies, it had taken a relatively conservative approach to the scope of the role; for example, one presentation described a very active MSL team with 2000 pre-licence discussions over an 8 month period for one product and an unprecedented

number of stakeholder comments for a National Institute for Health and Clinical Excellence (NICE) single technology appraisal for another product being attributed to the activity of the team. Further, the presentations also highlighted the value of the MSL role to the NHS. One presentation helpfully explained how a field-based MSL team could bring medical value to customers, including through publications, medical information, advisory boards and scientific updates. Servier also provided a company's job advertisement for an MSL role, from which it was clear that there was a proactive component pre-licence. Again, this illustrated Servier's conservatism compared with prevailing industry practice. The content of the MSL conference, together with the job description, supported the conclusion that the industry as a whole had understood the ruling in Case AUTH/1910/11/06 as a confirmatory signal for maintaining a field-based MSL team, an interpretation which was consistent with the provision made in the Code for the provision/exchange of non-promotional scientific information (Clauses 1.2, 3 and 21 as cited above).

Servier knew that its MLS role, which benefitted the NHS, also brought challenges due to the need to ensure that information with regard to unlicensed usage was strictly controlled. In developing the MLS role, Servier had thus ensured robust procedures, documentation, instructions and training.

Servier noted that its MLS team had no remit, mandate or incentive to promote any products (including licensed products). The team's main responsibility was to address spontaneous enquiries about Procoralan (ie the emphasis of the role was reactive in nature), as stated in the relevant job description. Secondary to that, and on a limited basis, other activities included management of non-interventional studies, delivery of medical and educational goods and services, training of other Servier staff, the non-promotional exchange of medical and scientific information (including involvement in advisory boards) and, to a small extent, advanced budgetary notification. In practice, the non-promotional role of the MLS team was achieved through the company structure, as well as rigorous training and robust policies.

With regard to the company structure, Servier noted that it did not mix promotional and non-promotional roles; the MLS team and the key account managers (KAMs, the only Servier employees with a selling remit) thus had completely separate reporting lines up to the chief executive officer, in each case with two levels of management between. The company organogram was provided. The MLS team reported to the national cardiovascular medical liaison manager, who in turn reported to the director of medical affairs. The KAMs, however, reported to their relevant therapy area divisional healthcare development manager each of whom reported to the director of healthcare development (the role closest to that of a national sales manager). This ensured that there was no overlap between the MLS role and KAM role. Servier submitted the respective job descriptions showed that the roles were entirely distinct. MLSs were not selected on the basis of their selling abilities but primarily for their medical/scientific knowledge and ability to communicate that knowledge (reference was made to the 'Indispensable Qualities' listed in the MLS (Cardiovascular) Job Description). In contrast, KAMs were selected on the basis of their selling ability, hence one of the indispensable qualities was to be 'Commercially astute and passionate about delivering results'.

Servier submitted that because the MLS role did not merge promotional and non-promotional functions, none of the material provided to the MLS team was promotional in nature. The Panel referred to three powerpoint presentations which were provided to the MLS team on request of medical enquiries: 'Ivabradine in Heart Failure'; 'Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial' and 'SHIFT-PRO Quality of Life Substudy'. Unfortunately, human error by an administrator which was not picked up by the signatories concerned, led to the first of these presentations being wrongly certified on a form intended for the certification of promotional items. In fact, the content was entirely non-promotional and should have been certified as such, consistent with the other two presentations; this error had now been rectified.

Servier had rigorous training procedures in place to ensure that the MLS team acted within the scope of its duties. Servier referred to the presentation 'Training on Advanced Budgetary Notification from National CV Medical Liaison Manager' as well as the relevant training and briefing materials. In particular, Servier referred to one of its MLS training presentations, a Code update which focussed on field-based medical information, which summarised the wide-ranging and important functions undertaken by the MLS team, from providing medical information in response to unsolicited enquiries to the organisation of advisory boards. The fundamental message of the presentation was that the MLS role was strictly non-promotional and therefore, whatever the task undertaken, it was critically important that the MLS team did not promote Servier's products. Servier submitted that the principles outlined in the presentation were upheld in the sound policies and procedures on which its MLS team was founded, and which were reflected in the operation of the team.

Servier submitted that advanced budgetary notification was a small but predetermined part of the MLS role and in-house data showed that advanced budgetary notification for ivabradine in heart failure had been very limited. Out of 116 advanced budgetary notification letters sent nationally since the SHIFT study results were published in September 2010, there had been 12 responses declining or deferring a meeting, and 36

requests for a meeting (which were indeed followed up by a meeting in each case) (January – June 2011). There were additionally 37 other requests for budget impact or cost effectiveness information arising spontaneously. Servier noted that the MLS team did not have any targets to meet in relation to advanced budgetary notification correspondence.

Servier submitted that the advanced budgetary notification material had been certified, which demonstrated that the company was concerned to ensure that communication regarding unlicensed usage was strictly controlled. The presentations demonstrating 'Cost effectiveness analysis of ivabradine in heart failure in a UK setting' and the 'Budget Impact Model based on results of SHIFT study' had been correctly certified as non-promotional, albeit only as a response following an unsolicited request. In its ruling, the Panel queried whether these materials constituted the data and modelling tools which the MLS in question had proactively offered; the answer was yes – Servier believed that these materials might be legitimately proactively disseminated in the context of advanced budgetary notification and should have been certified as such. This error had now been rectified.

Servier noted that with regard to its advanced budgetary notification procedure, the Panel queried whether the information about the product had been supplied early enough such that budget holders etc could be reasonably expected to act upon it. Servier noted that the supplementary information to Clause 3 of the Code stated: 'Health authorities and health boards and their equivalents, trust hospitals and primary care trusts and groups need to estimate their likely budgets **two to three years in advance** in order to meet Treasury requirements and there is a need for them to receive advance information about the introduction of new medicines, or changes to existing medicines, which may significantly affect their level of expenditure **during future years**' [emphasis added]. In spite of this wording, the current fundamental transformation within the NHS could not be ignored. Indeed, the structures explicitly referred to within the supplementary information to Clause 3.1 were being phased out, and corresponding revisions to the Code would be required. In Servier's view it was crucial for the industry to respond to the NHS need for budgetary information at the appropriate time; this was surely the purpose of the provisions on advanced budgetary notification. Only providing the information two to three years in advance, as referred to in the Code, did not meet the 'modern' needs of the NHS. By way of illustration, Servier referred to an ABPI email dated 29 July 2011 addressed to UK PharmaScan Champion Users which stated: 'You will probably be aware that the NHS financial planning cycle which determines budgetary spend for the year April 2012 – March 2013 will begin in September/October 2011. We have been given feedback from the NHS that current financial pressures mean that this timeline will be more important than ever this year for those in the NHS managing the entry of new medicines'. It therefore appeared that NHS financial planning cycle operated approximately 6-18 months in advance of budgetary spend. The heart failure indication for Procoralan originally expected in October/December 2011 or January/March 2012 was now anticipated in April/June 2012. Accordingly, Servier contended that by providing information to those responsible for making policy decisions on budgets between 15 months and even up to 6 months before the anticipated launch of Procoralan (on the basis of the original timeline forecast), the company had best fulfilled the function of advanced budgetary notification, ie to assist budget holders to determine budgetary spend. Accordingly, in answer to the Panel's query as to whether the information had been supplied early enough such that budget holders could be reasonably expected to act upon it, Servier believed that it had and reflected a proper partnership with the current, evolving NHS.

Servier noted that the Panel also queried whether the introduction of Procoralan for chronic heart failure would have a significant budgetary implication. Servier noted that significant was not defined in the Code; currently, NHS managers were experiencing a budget squeeze without precedent, and were perhaps themselves best placed to evaluate significance. Servier developed its advanced budgetary notification procedure in good faith, mindful of the current economic pressure on the NHS, and in the belief that the relevant budgetary impact estimates might be considered significant by NHS managers. Whilst Servier acknowledged that no details were provided in the access letter on the budgetary implication, Servier's budget impact model based on the results of SHIFT study showed a typical net annual cost of treating with ivabradine of £3,000-£9,000 per 100,000 head of population. The fact that half of all budgetary information calls were in response to spontaneous enquiries (37/73) strongly indicated that the NHS considered that spend on products/indications such as the one at issue to be significant.

Servier denied that it had promoted Procoralan for the unlicensed indication of heart failure.

Servier understood the Panel to have ruled of a breach of Clause 3.2 because the Panel considered that:

- Servier's advanced budgetary notification procedures did not meet the conditions set out in the supplementary information to the Code; and therefore
- Servier had 'arranged for its staff to proactively call upon health professionals and others to raise awareness of the use of Procoralan for an unlicensed indication';
  and therefore
- Servier's activities amounted to the promotion of Procoralan for an unlicensed indication.

Servier submitted that its advanced budgetary notification procedures complied with the Code.

However, even recognising that these procedures could be improved to provide specific information about the budgetary implications of the forthcoming indication in the access letter (a point which had emerged only as a result of the incident at issue and the company's review of the Panel's ruling, as well as the recent conclusion of Case AUTH/2327/6/10, but not previously obvious), Servier did not accept that its activities amounted to the promotion of Procoralan. The access letter included only factual information and it was clear that the purpose of the contact was to provide those who had a role in policy making or determining budgets with 'the relevant clinical and budgetary data relating to this product to assist your planning process'. Servier noted that legitimate targets for advanced budgetary notification were policy makers (who were often clinicians) and budget holders (often medicines management pharmacists). Again, the company's advanced budgetary notification procedure was designed in good faith, based on its understanding of the needs of the NHS, rational interpretation of the Code, previous rulings and the prevailing industry practice.

Servier disputed that it 'arranged for its staff to proactively call upon health professionals and others to raise awareness of the use of Procoralan for an unlicensed indication'. The Panel cited in evidence of this the fact that, in the last 6 months, the MLS in question had contacted 57 health professionals/budget holders about the use of ivabradine in heart failure. Fifty-seven contacts over a 6 month period would be very few indeed if Servier had, in fact, implemented a proactive, promotional communication programme as the Panel implied. Further, the Panel had wrongly assumed that the contacts in question were all proactive or related to advanced budgetary notification; this was not the case. Indeed, the majority of the work of the MLS team consisted of responding to unsolicited enquiries, with limited other types of contact. Servier considered that the Panel was misleading in its summary of the general guidance about responding to spontaneous enquiries about heart failure; it had implied that the guidance to KAMs referred only to one option in the event of enquiries on the SHIFT study: 'Key account managers were then instructed to say that they could not discuss this further but should further information be required the preferred option for follow-up was for a cardiovascular MLS to arrange a meeting'. However, the guidance actually showed that there were three options: a meeting with the MLS (cardiovascular), a phone-call from a scientific and medical information advisor or a meeting/phone-call with a medical advisor.

Servier noted that the Panel had stated that: 'The proactive provision of information by a pharmaceutical company about the unauthorized use of a medicine was very likely to be seen as promotion'. However, the majority of MLS contacts were reactive, and further, it could not be assumed that proactive contact about unlicensed indications was always promotional; this was why the supplementary information to Clause 3 specifically provided that medical and scientific information could be exchanged during the development of a medicine and that advanced budgetary notification might be performed. If all exchange was limited to responding to unsolicited enquiries then the supplementary information to Clause 3 would be redundant (Clause 1.2 stated that factual replies in response to unsolicited enquires were outside the scope of promotion).

Given the above, Servier strongly disputed that it had promoted Procoralan for an unlicensed indication. The Panel's conclusion did not correspond to the evidence and appeared to have been reached through a series of assumptions. The ruling provided no certainty for the company, which was of great concern to Servier in terms of the everyday operation of the MLS team.

Servier submitted that the Panel's ruling of a breach of Clauses 9.1 and 2 followed on from its conclusion that Servier had promoted Procoralan for an unlicensed indication. As Servier disputed the Panel's ruling of a breach of Clause 3.2, it also disputed the Panel's ruling of a breach of Clauses 9.1 and 2.

More specifically, with regard to Clause 9.1, Servier submitted that it had maintained high standards. These high standards were reflected in its policies relating to the role and activities of the MLS team, as well as its training material. In particular, whilst Servier recognised that its advanced budgetary notification procedures could be further tightened in light of the Panel's comments, it did not agree that it had failed to maintain high standards and considered that its interpretation of Clause 3 was reasonable in light of prevailing industry norms.

Servier was very concerned that the Panel had ruled a breach of Clause 2 of the Code, which should be reserved as a sign of particular censure. In Servier's view the Panel had based its conclusion of off-licence promotion on a series of assumptions triggered from an isolated and regrettable incident concerning one MLS, rather than on the evidence before it. The Panel stated that it 'considered that the activity amounted to a softening of the market for using Procoralan in heart failure'; but it did not specify what activity it was referring to (whether the advanced budgetary notification activity or other conjectured activity of the MLS team). If the Panel objected to the fact that Servier's access letter did not state the budgetary implications of the forthcoming heart failure indication, then the ruling of a breach of Clause 2 was disproportionate. Servier submitted that its advanced budgetary notification procedure was designed in good faith, based on the company's rational interpretation of the Code, previous Panel rulings and the prevailing industry practice. Accordingly, Servier did not believe that it has brought discredit upon, or reduced confidence in, the pharmaceutical industry.

As the MLS team did not have a promotional role,

either in principle or in practice Servier had appealed the ruling of a breach of Clause 15.2, which referred to the conduct of 'representatives'. Servier's MLS team did not fall within the definition of 'representatives', as they were not 'calling on members of the health professions and administrative staff in relation to the promotion of medicines' (Clause 1.6). Specifically, the MLS concerned did not call on health professionals to promote Procoralan for heart failure; he approached them within the framework of advanced budgetary notification, albeit clumsily, as detailed above.

Whilst Servier recognised that the emails at issue did not represent the high standards of Servier and were apparently misinterpreted, it did not accept that the correspondence amounted to the promotion of Procoralan for heart failure, or that this conclusion might be reached from the evidence. Servier submitted that the pre-licence context, the non-promotional role of the MLS and a sense of future planning were consistent in the communication thread. Engagement with the health professionals at issue was clearly in their respective roles of policy maker and budget holder. The purpose of the communication was to obtain information on appropriate contacts in order to approach them in respect of advanced notification of ivabradine for heart failure, as evidenced by the written statement from the MLS concerned (a copy was provided). The MLS concerned was referred to each contact by the preceding one, commencing with the chief executive officer. Servier noted that the email title 'Ivabradine in heart failure' was not written by the MLS, but added by one of the contacted health professionals who unfortunately jumped to the conclusion that the email thread was promotional, which did not appear reasonable in the context, and particularly given that the MLS stated up-front that he was not part of the sales force and had clearly entered into the correspondence in good faith. Servier therefore considered that the Panel's ruling of a breach of Clause 3.2 was disproportionate.

Servier submitted that this case has taught it that, even with robust procedures and training, unfortunate incidents might occur. Servier fully stood by the important role played by its MLS team, as testified by its commitment to strengthen yet further its policies and procedures relating to the MLS team. To this end, Servier had:

- In good faith suspended advanced budgetary notification, pending the outcome of the appeal;
- Amended human errors of certification and appropriately briefed all Servier staff and contractors concerned with Code compliance and
- Introduced a new requirement that all MLS emails to health professionals (including those in commissioning groups) were copied to the national MLS manager. These new processes were intended to ensure standardised communication and support compliance.

For the reasons explained above, Servier appealed the Panel's rulings of breaches of Clauses 2, 3.2, 9.1 and 15.2 relating to the activities of the company, as well as Clause 3.2 relating to the activities of the individual MLS concerned.

COMMENTS FROM THE COMPLAINANT

The complainant considered that his original comments stood. The offer of 'pathway development' in heart failure was a way in to discuss the findings of the SHIFT study and therefore get commissioners interested in using an unlicensed and contraindicated medicine in heart failure.

APPEAL BOARD RULING

The Appeal Board noted that Clause 3 prohibited promotion of a medicine prior to the grant of its marketing authorization and also required that promotion of a medicine was in accordance with the terms of its marketing authorization and not inconsistent with its SPC. The supplementary information to Clause 3 set out guidance in relation to certain situations including the provision of advanced notification of new products or product changes. This supplementary information included a requirement that such information must include the likely cost and budgetary implications and this must be such as to make a significant difference to the likely expenditure of health authorities, trusts and the like.

The Appeal Board noted that the emails at issue sent by the MLS did not discuss the anticipated cost or the budgetary implications of using Procoralan for heart failure. The Appeal Board noted that one of the MLS's emails stated that 'I have seen many consultant cardiologists in the [local] region and the responses have been very positive. In some areas clinicians are already using the product (off licence) in heart failure. As a consequence I felt it appropriate to make contact, to ensure that as the director of clinical transformation, you would have an opportunity to be brought up to date with the most recent data that we have'. The Appeal Board considered that the very positive description of the heart failure indication in the absence of any discussion either of the budgetary implications or the significance of the difference in expenditure meant that the MLS had promoted Procoralan for an unlicensed indication. The email in question could not take the benefit of the exemption for advance notification set out in the supplementary information to Clause 3.1. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful.

The Appeal Board noted that 'representative' was defined in Clause 1.6 of the Code as 'a representative calling on members of the health professions and administrative staff in relation to the promotion of medicines.' It considered that its ruling that the product had been promoted for an unlicensed indication did not mean that it considered that the MLS job description described a representative's role as defined in Clause 1.6. The

Appeal Board thus ruled no breach of Clause 15.2 as this clause applied to the conduct of representatives. The appeal on this point was successful.

The Appeal Board noted that advanced information about an unlicensed indication could only be supplied if such use of the product had a significant budgetary implication and the information included details of the likely cost and budgetary implication. The relevant supplementary information to Clause 3.1 set out detailed conditions. The Appeal Board noted Servier's submission for the appeal that its Budget Impact Model, based on the results of the SHIFT study (Swedburg *et al*), showed a typical net annual cost of treating heart failure with Procoralan of £3,000-£9,000 per 100,000 head of population. The Appeal Board noted in the email correspondence the head of prescribing and medicines management stated that the estimated cost to the PCT of using Procoralan in a suitable population was around £75,000/year but there would be 'therapeutic creep' and so the cost would be considerably more. The head of prescribing and medicines management also stated that the patients in the study were not on optimum doses of beta-blocker. The Appeal Board considered that NHS managers were likely to regard such potential increases in budgetary requirements as significant. This was particularly so given the current economic environment. The Appeal Board considered that the licence extension application for Procoralan for heart failure satisfied the condition in the supplementary information to Clause 3.1 that advanced notification information might be provided for '… a product which is to have a significant addition to the existing range of authorized indications …'.

The Appeal Board did not consider that starting the advanced notification in August/September 2010 for changes to the licence expected by the end of 2011 was unacceptable. The Appeal Board noted Servier's submission for the appeal that the licence was now expected in April/June 2012. The Appeal Board noted the access letter discussed the ivabradine licence application to add an indication for chronic heart failure. The letter detailed the current licensed indication and stated that the Code advised that advanced budgetary information might be provided to policy influencers and those responsible for budgetary decisions to aid future planning. The Appeal Board considered that the purpose of the letter was to determine if recipients were responsible for budgetary decisions and if so to provide '…the relevant clinical and budgetary data relating to this product to assist your planning process'. The letter also stated that the author intended to contact the recipient to organise a meeting. Servier submitted that from the 116 letters sent there had been 36 requests for a meeting and another 37 meeting requests had arisen spontaneously.

The Appeal Board considered that advanced notification was a difficult area and care was needed to satisfy the relevant requirements of the supplementary information to Clause 3.1. The Appeal Board was concerned about some of the claims made in material used by the MLSs and also about their proactive contact of key opinion leaders. Nonetheless the Appeal Board did not consider that the company's activity amounted to the promotion of Procoralan for an unlicensed indication. The Appeal Board also noted that the complainant had emphasised the role of the individual MLS as evidenced by the email trail rather than activities undertaken by the company. The Appeal Board ruled no breach of Clause 3.2. The appeal on this point was successful.

The Appeal Board noted the rulings of a breach of the Code in relation to the MLS in question. The Appeal Board considered that Servier should have more closely controlled its MLS team. High standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

During its consideration of this point the Appeal Board noted Servier's recent decision that emails sent by the MLS team be copied to their manager but queried whether this on its own introduced sufficient control.

The Appeal Board noted its rulings above and thus considered that this case did not warrant a ruling of a breach of Clause 2 and no breach of that clause was ruled. The appeal on this point was successful.

Given its rulings the Appeal Board decided to take no further action in relation to the Panel's report made in accordance with Paragraph 8.2 of the Constitution and Procedure.

Complaint received **14 June 2011**

Case completed **10 October 2011**

CASE AUTH/2418/7/11

PHARMACIST v ASTELLAS PHARMA

Promotion of Protopic

A pharmacist complained about a Protopic (tacrolimus) leavepiece issued by Astellas Pharma. The front cover featured the claim '142 days without a major eczema flare? That's a whole British summer' above a photograph of a woman standing in a field, wearing sandals, knee-length shorts and a vest top. The weather appeared to be blustery and cold.

The complainant submitted that the Protopic summary of product characteristics (SPC) stated that skin exposure to sunlight should be avoided when using the medicine. In that regard the complainant alleged that the leavepiece promoted Protopic in a manner inconsistent with its SPC and misleadingly implied that it could be used in the summer on skin exposed to sunlight. The complainant further alleged that the promotion failed to maintain high standards.

The detailed response from Astellas is given below.

The Panel noted the photograph on the front cover of the leavepiece and although the weather conditions were largely overcast, images of the same woman's face on pages 2 and 5 appeared to reflect sunlight.

Page 4 of the leavepiece referred to patients with frequently-flaring eczema in visible and delicate areas and page 2 referred to the use of Protopic when there were concerns about stepping up to a more potent corticosteroid. Two photographs in the leavepiece featured only the patient's head and shoulders. In the Panel's view there was thus an implication that at least some of the patient population at issue were those with eczema on the face and neck. An explanation of how to use Protopic specifically referred to the amount of ointment to be applied to the face and neck.

Section 4.4 of the Protopic SPC, Special warnings and precautions for use, stated that exposure of the skin to sunlight should be minimised. Physicians should advise patients on appropriate sun protection methods, such as minimisation of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing. The Panel noted that in its response, Astellas had not referred to 'covering of the skin with appropriate clothing'.

The Panel noted Astellas' submission that the patient depicted was demonstrating her well-controlled eczema. The Panel accepted that patients who had achieved 142 days without a major eczema flare might want to demonstrate such control of the condition but considered that any such depiction in promotional material had to comply with the Code.

The Panel noted that Astellas referred to avoiding extreme summer conditions and overt sunshine and considered that such references did not fairly reflect the special warning in the SPC about minimising exposure of the skin to sunlight. The Panel noted that skin might be exposed to sunlight even in overcast conditions.

The Panel considered that the front cover of the leavepiece implied that the patient did not have to be concerned about exposure to sun and that was not so: this was inconsistent with the particulars listed in the SPC and a breach of the Code was ruled.

Upon appeal by Astellas, the Appeal Board noted that the leavepiece was directed at GPs and pharmacists. Protopic had not been actively promoted to either group in the last five years. The leavepiece was approved for use in May 2011 and would thus be used through the summer. The SPC stated that Protopic treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis.

The Appeal Board noted that the advice in the SPC about minimisation of skin exposure to sunlight and the use of sun protection methods was based on a theoretical potential risk of malignant skin changes (skin malignancies had been reported in association with oral tacrolimus treatment).

The Appeal Board noted Astellas's comment that it was not possible to cover the face with appropriate clothing but considered that physicians could advise relevant patients to wear a sun hat. The Astellas representatives agreed that if the leavepiece had depicted overt sunshine then a sun hat would have been appropriate; they stated that the patient depicted might have already applied sunscreen. The Appeal Board noted the three photographs of the patient (on the front cover and pages 2 and 5) were not the same and considered that the photograph on page 5 of the leavepiece reinforced the impression that the patient was wearing minimal clothing on a sunny day.

The Appeal Board was concerned to note that research had shown that prescribers would not ordinarily advise Protopic patients about sun protection. The Appeal Board considered that

such advice was an important aspect to the appropriate use of Protopic. The leavepiece was directed to an audience which might not be wholly familiar with the product and was about patients being able to expose skin in the summer. The Appeal Board considered that companies had a responsibility to ensure that their medicines were correctly used and in that regard it considered that in the circumstances there should be some acknowledgement of the SPC warning. The prescribing information was inadequate in this regard. In the Appeal Board's view the images in the leavepiece were inconsistent with the particulars listed in the Protopic SPC. The Appeal Board thus upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

The Panel noted that the complainant had also alleged that the leavepiece misleadingly implied that Protopic could be used in the summer on areas of skin exposed to sunlight. The Panel noted that Section 4.2 of the SPC stated that Protopic ointment might be used on any part of the body, including the face, neck and flexure areas, except on mucous membranes. There was no prohibition on using Protopic on areas of skin exposed to sunlight such as the face although of course the special warning in Section 4.4 should be borne in mind. The Panel did not consider the leavepiece was misleading on the narrow point alleged; no breach of the Code was ruled which was upheld upon appeal.

The Panel considered that its ruling of a breach of the Code above adequately covered its concerns about this matter; the circumstances did not warrant a further ruling with regard to high standards. No breach was ruled which was upheld upon appeal.

A pharmacist complained about a leavepiece (ref: PRO11003UK) for Protopic (tacrolimus) issued by Astellas Pharma Ltd. The front cover of the leavepiece featured the claim '142 days without a major eczema flare? That's a whole British summer' above a photograph of a woman standing in a field and wearing strappy sandals, knee-length denim shorts and a vest top. The weather appeared to be blustery and cold.

COMPLAINT

The complainant noted that the woman had exposed skin on her lower legs, arms and around her neckline as well as her face.

The complainant considered that the wording and picture inferred that Protopic did not carry a specific warning that skin exposure to sunlight should be avoided when using the medicine however, this was a specifically worded precaution in the summary of product characteristics (SPC).

The complainant alleged that the leavepiece promoted Protopic in a manner inconsistent with its SPC in breach of Clause 3.2. The complainant further alleged a breach of Clause 7.2 because the leavepiece misleadingly implied that Protopic could be used in the summer on areas of skin exposed to sunlight. Finally, the complainant alleged that the promotion failed to maintain high standards in breach of Clause 9.1.

RESPONSE

Astellas stated that patient safety was its highest priority and the company took its obligations to the letter and spirit of the Code extremely seriously. The company explained that the focus of the campaign was the prevention of eczema flares (two single applications of Protopic per week to areas usually affected). The leavepiece, to be given to health professionals by sales representatives, supported this message. Care was taken when composing the scene on the front of the leavepiece to incorporate noticeably dark clouds and dull tones to generate overcast conditions, avoiding overt sunshine. This was balanced by the presence of several people in the background who were dressed in line with those readily recognisable poor weather conditions (supporting the use of the ironic statement: 'That's a whole British summer'). The patient featured in the photograph was taking the opportunity to demonstrate her well-controlled eczema at a time of year when her attire would ordinarily be deemed more appropriate to summer conditions. Astellas noted that the patient was not wearing minimal clothing eg swimwear or necessarily demonstrating excessive sun exposure eg through sunbathing.

Astellas noted the complainant's submission that the Protopic SPC stated that skin exposure to sunlight should be avoided. This was incorrect. The SPC actually stated 'Exposure of the skin to sunlight should be minimised'; it did not state that exposure of the skin to sunlight should be avoided.

If the depicted weather included extreme summer conditions, Astellas considered that the patient featured would still not necessarily be demonstrating irresponsibly excessive sun exposure through either her attire or associated activities.

Astellas considered that it was unreasonable to expect eczema sufferers (treated with Protopic) to be dressed in clothing covering the entire body when outdoors, regardless of the season/climate.

Astellas noted that Section 4.2 of the SPC stated 'Protopic ointment may be used on any part of the body, including face, neck and flexure areas, except on mucous membranes'.

The use of topical calcineurin inhibitors such as Protopic on the face was specifically referred to in a National Institute for Health and Clinical Excellence (NICE) guideline. TA82 'Tacrolimus and pimecrolimus for atopic eczema' stated: 'Tacrolimus is applied as a thin layer to affected areas of the skin twice daily and may be used on any part of the body, including the face, neck and flexural areas'.

The Protopic SPC further stated 'Physicians should advise patients on appropriate sun protection methods, such as the minimisation of time in the sun, use of a sunscreen product…' and Astellas submitted that it always advocated this course of action.

The focus of the campaign was the prevention of eczema flares in particular, on visible, delicate areas such as the face where the use of sunscreen application and minimisation of time in the sun were the only practical options for minimisation of skin exposure to sunlight.

Astellas refuted the allegation that the campaign implied that Protopic could be used during the summer on areas of sun exposed skin. There was no contraindication to the use of Protopic, either during the summer or on areas of sun exposed-skin. As noted above, the Protopic SPC stated 'Exposure of the skin to sunlight should be minimised'. It did not state that exposure of the skin to sunlight should be avoided. Similarly, there was no contraindication to the use of the product either in the summer or on sun exposed areas of skin.

In summary, Astellas denied a breach of Clauses 3.2, 7.2 or 9.1.

PANEL RULING

The Panel noted that the front cover of the leavepiece depicted a woman dressed in a vest top, long shorts and flat strappy sandals, holding a pair of binoculars whilst standing in front of a large, open field that appeared to be a campsite. Figures in the background also wore long shorts but were each wearing long sleeved jackets. The woman was thus wearing less clothing and consequently exposing more skin than those around her. The sky was overcast with rain clouds threatening to the right of the picture but with much lighter clouds on the horizon to the left, to which the figure was facing. The accompanying text '142 days without a major eczema flare? That's a whole British summer' made clear that the photograph depicted the variable weather conditions of a British summer. An image of the same woman's face on pages 2 and 5 of the leavepiece appeared to reflect sunlight although the background was still slightly overcast.

Page 4 of the leavepiece referred to patients with frequently-flaring eczema in visible and delicate areas and page 2 referred to the use of Protopic when there were concerns about stepping up to a more potent corticosteroid. Two photographs in the leavepiece featured only the head and shoulders of the depicted patient. In the Panel's view there was thus an implication that at least some of the patient population at issue were those with eczema on the face and neck. A diagram on page 3 explaining how to use Protopic specifically referred to the amount of ointment to be applied to the face and neck.

Section 4.4 of the Protopic SPC, Special warnings and precautions for use, stated that exposure of the skin to sunlight should be minimised. Physicians should advise patients on appropriate sun protection methods, such as minimisation of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing. The Panel noted that in its response, Astellas had not referred to 'covering of the skin with appropriate clothing'.

The Panel noted Astellas' submission that the patient depicted in the leavepiece was taking the opportunity to demonstrate her well-controlled eczema. The Panel accepted that patients who had achieved 142 days without a major eczema flare might want to demonstrate such control of the condition but considered that any such depiction in promotional material had to comply with the Code.

The Panel noted that Astellas referred to avoiding extreme summer conditions and overt sunshine and considered that such references were not a fair reflection of the special warning about minimising exposure of the skin to sunlight in Section 4.4 of the SPC. The Panel noted that skin might be exposed to sunlight even in overcast conditions.

The Panel considered that the front cover of the leavepiece implied that the patient did not have to be concerned about exposure to sun and that was not so: this was inconsistent with the particulars listed in the Protopic SPC and a breach of Clause 3.2 was ruled.

The Panel noted that in addition the complainant had also alleged that the leavepiece misleadingly implied that Protopic could be used in the summer on areas of skin exposed to sunlight. The Panel noted that Section 4.2 of the SPC stated that Protopic ointment might be used on any part of the body, including the face, neck and flexure areas, except on mucous membranes. There was no prohibition on using Protopic on areas of skin exposed to sunlight such as the face although of course the special warning in Section 4.4 should be borne in mind. The Panel did not consider the leavepiece was misleading on the narrow point alleged; no breach of Clause 7.2 was ruled.

The Panel noted its rulings above and considered that its ruling of a breach of Clause 3.2 adequately covered its concerns about this matter and the circumstances did not warrant a further ruling in relation to Clause 9.1; no breach of Clause 9.1 was ruled.

APPEAL BY THE COMPLAINANT

The complainant noted that although a breach of Clause 3.2 had been ruled Astellas had defended the leavepiece noting careful composition of the background to the front page image to include 'overcast conditions, avoiding overt sunshine'. This, however, was not the case in the image on the reverse of the leavepiece on the section titled 'References' where the face of the woman was apparently in direct sunlight. The overcast

conditions were therefore inconsistent throughout the piece.

The complainant understood the ironic use of 'British summer' however, just as there were periods of inclement weather there were often long, warm, sunny spells. Clinicians were not warned anywhere in the leavepiece, other than in the prescribing information, that exposure of the skin to sunlight should be minimised. In the complainant's view, it was imprudent to link the promotion of a product that contained such a warning to 'summer'.

The complainant noted that the Panel ruled that the leavepiece was not misleading by implication as the SPC included no prohibition to use on areas of skin exposed to sunlight. The complainant noted that the SPC contained a specific special warning advising that exposure of the skin to sunlight should be minimised and that physicians should advise patients on sun protections methods such as minimisation of time in the sun, sunscreen and appropriate clothing.

Although the leavepiece did not depict an individual with a less than appropriate level of clothing there was no mention or indication of sunscreen or sunlight exposure limitation by time. For example, the woman depicted could have been portrayed walking from outdoors to indoors or applying sunscreen. The complainant also noted that in the entry for tacrolimus, the BNF stated in the cautions section 'UV light (avoid excessive exposure to sunlight and sunlamps)'.

The complainant therefore alleged that the spirit of the photographs in the leavepiece was inconsistent with the safety message that skin exposure to sunlight (and other sources of UV light) should be minimised and that physicians needed to advise patients using these products to employ protective measures such as reduce skin exposure time, cover up with clothing and apply sunscreen.

The complainant noted that the Panel ruled that a breach of Clause 3.2 adequately covered this complaint and as such it did not rule a breach of Clause 9.1.

The complainant was not entirely familiar with PMCPA procedures but he wondered why this clause was not examined further with acceptance that a breach of Clause 3.2 was adequate. It would be more appropriate to rule that high standards had been maintained or otherwise independently of a review of other clauses. However, as the complainant had already stated he was not fully aware of the PMCPA's inner workings so this might be common practice, in which case the complainant noted that Astellas asserted that it made patient safety its highest priority and also stated that it would always advocate that physicians advised patients on appropriate sun protection methods. While the complainant could not dispute either of these assertions in general terms, in specific regard to this leavepiece there was no explicit mention anywhere in the leavepiece, other than in the prescribing information, that this medicine had any cautions on use relating to UV light, which seemed at odds with the use of a promotional theme based on the British summer (albeit ironically). As noted above it seemed the Panel noted too, there was an overt picture of a woman's face bathed in sunlight within this leavepiece.

In summary, the complainant stated that since Astellas had appealed the ruling of a breach of Clause 3.2, there was perhaps room to review all three clauses originally alleged to be in breach.

COMMENTS FROM ASTELLAS

With respect to the ruling of a breach of Clause 3.2, Astellas submitted that it had responded fully to the complainant's allegations and the findings of the Panel in its original response and subsequent appeal.

In relation to the appeal of no breach of Clause 7.2 (promotion which misleadingly implied that Protopic could be used during summer months on areas of sun exposed skin) and Clause 9.1 (failure to maintain high standards), Astellas submitted that it had responded to these allegations in detail previously. Astellas again noted that the SPC did not state that exposure of the skin to sunlight should be avoided. Similarly, there was no contraindication to the use of Protopic, either in the summer or on sun-exposed areas. Astellas submitted that the imagery used in this case was fully consistent with the SPC, specifically in relation to Section 4.4, 'Special warnings and precautions for use'.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant had no further comments.

APPEAL BY ASTELLAS

Astellas considered that the imagery used in the leavepiece was consistent with the SPC, specifically in relation to Section 4.4, 'Special Warnings and Precautions for Use'.

In relation to the specific 'Special Warning or Precaution for Use' the Protopic SPC stated the following: 'Physicians should advise patients on appropriate sun protection methods, **such as** minimisation of time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing' (emphasis added). It did not state that exposure of the skin to sunlight should be avoided, rather that these methods should be recommended as examples of measures to minimise exposure to sunlight. Obviously, it was not possible to apply all of these measures, in particular appropriate clothing, in cases where the treated area was the face.

As noted by the Panel, the focus of the campaign at issue was the treatment of sensitive areas such as

the face and neck where potent steroids might not be tolerated due to potential side effects. In this respect, the only practical sun protection methods which could be applied to the face were, as stated in the Protopic SPC, the use of sunscreen or minimisation of time in the sun. These measures were not necessarily practical steps which could be depicted in the imagery. Similarly, other additional specific 'Special warnings and precautions for use' were not necessarily possible to address in the imagery.

Astellas submitted that the imagery was not inconsistent with the SPC in this respect.

Astellas noted the Panel's observation that the image of the woman's face on pages 2 and 5 of the leavepiece appeared to reflect sunlight. It was important to clarify that this image was the same image as used on the front cover of the leavepiece on the background of the dull, overcast conditions and dark clouds.

Specifically, the composition of the scene on the front cover included the following intentional elements:

- dark clouds and dull tones to generate overcast conditions
- no depiction of the sun
- the inclusion of several reference figures dressed appropriately for the poor weather conditions. The Panel noted that 'the woman was thus wearing less clothing and consequently exposing more skin than those around her'. The bystanders in the scene were covered up because of the poor weather, not to minimise exposure to sunlight. They would not require this degree of weatherproof clothing if the conditions matched the attire of the woman in focus. Indeed, this was the ironic basis for the headline on the front cover 'That's a whole British summer'
- the Panel noted that 'skin might be exposed to sunlight even in overcast conditions'. Following implementation of the appropriate outlined sun protection measures, eczema patients treated with Protopic were at liberty to go outdoors though not necessarily in full length items of clothing irrespective of the climate/conditions. Once again, the SPC did not state that sunlight should be avoided.

Astellas was conscious of the impact of any chronic condition on patients who were prescribed its products. In devising this campaign, Astellas undertook market research to understand the impact of eczema upon patients' lives. As a result of the many associated negative psychological consequences, in depicting the typical patient and their surroundings, Astellas was keen to emphasise the importance of patient confidence and to avoid the exclusion of this patient group from the usual activities of daily life including the freedom to wear clothing which would (ordinarily) be appropriate to the conditions, and not exceptional to the clothing of those around them.

Astellas submitted that it was not a requirement of the Code to list all precautions and special warnings in an SPC on advertisements other than in the prescribing information. Astellas took patient safety extremely seriously and care had been taken with the imagery to ensure it was consistent with the SPC. Astellas considered that it was not the case that 'the leavepiece implied that the patient did not have to be concerned about exposure to the sun'. As described in detail above, the scene was neither sunny, nor was the patient dressed in minimal clothing or necessarily failing to adhere to the sun protection advice deemed appropriate for her treatment and as recommended in the SPC to be advised by the physician.

In summary therefore, the essence of this case was a difference of opinion between Astellas and the Panel. Astellas submitted that the imagery did not promote the use of Protopic ointment in a manner inconsistent with the SPC. Astellas had taken reasonable care to depict a dull and overcast day and it hoped the Appeal Board agreed with its view and rule no breach of Clause 3.2.

COMMENTS FROM THE COMPLAINANT

The complainant referred to their letter of appeal and had nothing further to add.

APPEAL BOARD RULING

The Appeal Board noted from the Astellas representatives that the leavepiece was directed at general practitioners and pharmacists. Protopic had not been actively promoted to either group in the last five years. The leavepiece was approved for use in May 2011 and would thus be used through the summer months. The SPC stated that Protopic treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis.

The Appeal Board noted the statement in the SPC that 'Exposure of the skin to sunlight should be minimised … Physicians should advise patients on appropriate sun protection methods, such as minimisation of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing'. The Appeal Board noted from the Astellas representatives that the SPC advice was based on a theoretical potential risk of malignant skin changes (skin malignancies had been reported in association with oral tacrolimus treatment).

The Appeal Board noted Astellas' comment that it was not possible to cover the face with appropriate clothing but considered that physicians could advise relevant patients to wear a sun hat. The Astellas representatives agreed that if the leavepiece had depicted overt sunshine then a sun hat would have been appropriate. The Astellas representatives stated that the patient depicted might have already applied sunscreen. The Appeal Board noted the three photographs of the patient (on the front cover and pages 2 and 5) were not the same and considered

that the photograph on page 5 of the leavepiece reinforced the impression that the patient was wearing minimal clothing on a sunny day.

The Appeal Board was concerned to note from the company representatives that according to its research, prescribers would not ordinarily advise Protopic patients about sun protection methods. The Appeal Board considered that sun protection advice was an important aspect to the appropriate use of Protopic. The leavepiece at issue was directed to an audience which might not be wholly familiar with the product and was all about patients being able to expose skin in the summer months. The Appeal Board considered that companies had a responsibility to ensure that their medicines were correctly used and in that regard it considered that in the circumstances there should be some acknowledgement of the SPC warning. The prescribing information was inadequate in this regard. In the Appeal Board's view the images in the leavepiece were inconsistent with the particulars listed in the Protopic SPC. The Appeal Board thus upheld the Panel's ruling of a breach of Clause 3.2 of the Code.

The Appeal Board noted that the complainant had alleged that the leavepiece misleadingly implied that Protopic could be used in the summer on areas of skin exposed to sunlight. The Appeal Board noted that exposure to sunlight was not prohibited although patients should be advised about minimisation of exposure to the sun. The Appeal Board did not consider the leavepiece was misleading on this narrow point as alleged. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.2. The appeal on this point was unsuccessful.

The Appeal Board noted its rulings above and considered that it did not warrant a further ruling in relation to Clause 9.1. The Appeal Board upheld the Panel's ruling of no breach of Clause 9.1. The appeal on this point was unsuccessful.

Complaint received **24 June 2011**

Case completed **10 October 2011**

MEMBER OF THE PUBLIC v BIOGEN IDEC

Tysabri on-line advertisement

A member of the public complained about an advertisement for Tysabri (natalizumab) published in the online version of The Telegraph newspaper. Tysabri was one of Biogen Idec UK's medicines. The complainant stated that it was strange that this prescription only medicine (POM) was advertised to the public. A screenshot showing the advertisement was provided.

The detailed response from Biogen Idec is given below.

Following Biogen Idec's response that the advertisement was from the US and not intended for a UK audience, the complainant was asked for further information. The complainant could not think of any website that would lead to receipt of the advertisement while reading a UK newspaper online. The complainant was British and resided in the UK.

The Panel noted that the material at issue was a retargeted advertisement placed by Biogen Idec's US affiliate and that Biogen Idec in the UK had no role in the creation or publication of the advertisement. The Panel noted that in accordance with an established principle under the Code, Biogen Idec UK was responsible for the acts and omissions of its US affiliate that came within the scope of the Code.

The Panel noted that the complainant, a UK resident, had seen an advertisement for a POM published on the UK website of a British daily newspaper. The Panel considered that the link to the UK was such that the matter came within the scope of the Code.

The Panel noted that an internet protocol (IP) address was the unique number assigned to every computer or connection to the internet. Biogen Idec submitted that the complainant must have seen the Tysabri advertisement on a US site before she could be served the same advertisement on another site, in this case The Telegraph online. According to Biogen Idec the complainant would have had a US IP address or server.

The Panel also queried whether, irrespective of its comments above about retargeting, The Telegraph online was an appropriate forum on which to re-serve a targeted US advertisement for a POM. Both its readership and content were relevant. The Telegraph was a British newspaper which published UK and global news from a UK perspective. The Panel noted that both within Western Europe and globally in June 2011 the largest single absolute number of hits to the UK website was from the UK. In June 2011 48% of hits were from the UK and 23% were from the US. The Panel noted Biogen Idec's submission that the retargeting criteria that qualified The Telegraph as a suitable site for US based IP address users were the type of audience the site catered for, overall content and demographics.

The complainant, a UK resident, had seen a US advertisement for a POM on a website for a UK daily newspaper. The complainant did not know her IP address. The Panel noted its comments above about retargeting. Overall the Panel considered that retargeting did not appear to be sufficiently sophisticated to ensure compliance with the Code. The Panel considered on balance that a user's IP address or location of the user's server was not a sufficiently precise surrogate for the user's status in the UK so as to ensure not promoting a POM to the public. The Panel considered that irrespective of whether the complainant had a UK or US IP address, the publication of the retargeted US Tysabri advertisement in The Telegraph on line as seen by the complainant constituted promotion of a POM to the public. A breach of the Code was ruled. High standards had not been maintained. A breach of the Code was ruled. These rulings were appealed by Biogen Idec.

Overall, the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure. Some attempt, albeit unsatisfactory, had been made to ensure a link to a US audience. No breach of Clause 2 was ruled. This ruling was not appealed.

The Appeal Board noted Biogen Idec's submission that advertisement retargeting ie re-serving an internet user with an advertisement on a different website from that on which they had viewed it before, was based on geographic-specific IP addresses. This type of retargeting was standard for the internet as a whole and was how Biogen Idec US could retarget its advertisements only to those with a US IP address. The Telegraph website, telegraph.co.uk, (when accessed via a US IP address) was included in the retargeting package purchased by Biogen Idec US.

The Appeal Board noted the submission that the Internet Service Provider (ISP), the means by which access to the internet was provided, could not determine the user's geographical location. It was possible to connect to a US IP address via a UK ISP.

The Appeal Board noted Biogen Idec's submission that, with 99.9% certainty, to have seen the advertisement at issue the complainant would have had to have first seen it on the Tysabri.com website via a US IP address. Only then would the complainant have been retargeted with the advertisement on The Telegraph website when this was also accessed via the same US IP address.

There appeared to be inconsistencies between the written submissions and Biogen Idec's presentation at the appeal as to whether the reader had to visit a specific US site, previously responded to a US Tysabri advertisement or merely have seen a US Tysabri advertisement.

At the appeal hearing Biogen Idec's representatives stated that the advertisement in question could only be viewed if the reader's IP address had been 'retargeted'. In order for this to happen two conditions had to be met: firstly the reader must voluntarily have accessed a US Tysabri website via a US IP address and secondly the reader must have then subsequently viewed another website using the same US IP address. The slide stated that thus the advertisement could only be seen if the reader had viewed at least two US websites (including specifically the Tysabri US website) using a US IP address. This was described as a core element of Biogen Idec's US 'media buy' package for this activity.

The Appeal Board further noted from Biogen Idec's submission that it would expect the majority of internet users in the UK to have a UK IP address. Exceptions might include those who worked for a US company and accessed the internet via their employer's internet connection or those who had installed specialist software. The complainant had not stated that either of these applied.

The Appeal Board considered that it was confusing that an advertisement for a POM was linked to a .co.uk website as it would appear to some readers (albeit those with US IP addresses) that the advertisement was a part of the .co.uk website when in fact that was not so.

The Appeal Board considered that advertising POMs to the public was a serious matter. However the complainant had the burden of proving his/her complaint on the balance of probabilities and in that regard had provided limited information and had not confirmed his/her IP address.

The Appeal Board considered that the complainant had not established his/her case on the balance of probabilities and thus ruled no breach of the Code. The Appeal Board did not consider that Biogen Idec had failed to maintain high standards. No breach of the Code was ruled. The appeal on both points was successful.

A member of the public complained about an advertisement for Tysabri (natalizumab), a prescription only medicine, published in the online version of The Telegraph (www.telegraph.co.uk) on 24 June 2011. Tysabri was one of Biogen Idec UK Limited's medicines.

COMPLAINT

The complainant stated that it was strange that this prescription only medicine was advertised to the public and alleged breaches of Clauses 2, 9.1 and 22.1. The complainant provided a screenshot of the page in question.

RESPONSE

Biogen Idec stated that the UK affiliate did not promote prescription only medicines to the public. The advertisement image sent by the complainant was of poor quality, however based on the wording deciphered from the indication and important safety information from the advertisement Biogen Idec confirmed it was produced in the US, where it was advertised to the public in accordance with local law. It was not intended for a UK audience. It was not created nor placed on the internet by Biogen Idec UK. Given this it did not have copies of certification or references to provide, and the UK summary of product characteristics was not applicable to US promotional material.

Biogen Idec UK contacted The Telegraph online advertising department to ask for clarification as to whether geographical location determined which advertisements could be viewed online. It confirmed that advertisement targeting was based on internet protocol (IP) address or server location. Biogen Idec understood that the IP address was a unique number assigned to every computer or connection to the internet. The numbers were grouped by geographical region. UK targeted advertisements could only be seen from a UK IP address or server. Similarly, US targeted advertisements could only be seen from a US IP address or server. Biogen Idec was unable to locate the advertisement in question when it accessed the newspaper website and the relevant page from a UK IP address or from a UK internet service provider.

The Telegraph website provided media purchasing inventory to a US company that specialised in media audience targeting platforms. This company was one of the service providers of Biogen Idec's US affiliate. Consumers had to have seen the Tysabri advertisement on a US site before they could be served the same advertisement on another network site targeted by the media audience targeting service (a method known as 'retargeting'). Biogen Idec's media buy for this was a US only initiative. The US media audience targeting platform service provider confirmed that the complainant who saw the Tysabri banner advertisement on www.telegraph.co.uk would have had a US IP address. The service provider also

confirmed that 99.9% of its retargeting activities had a US IP address (100% was impossible to claim due to the possibility of computer registration error).

Biogen Idec stated that if, notwithstanding the accessibility of web content as described above, the complainant asserted that he/she did view the website page from a UK server or IP address, evidence would be needed to support this. The complainant cited breaches of Clauses 2, 9.1 and 22.1 of the Code. To the extent that the advertisement was viewed from the US or via a non-UK server or IP address, Biogen Idec's view was that the Code was not intended to cover legitimate extra-territorial promotional activities by non-UK entities who were not within the jurisdiction of the Code and whose activities were not intended to be directed or routed to a UK audience under Clause 1.1.

In response to a request for further information from the Panel, Biogen Idec stated that its US affiliate confirmed that the retargeting criteria which qualified The Telegraph as a suitable site for advertising online was based on the fact that the site was aligned to Tysabri inventory quality standards (type of audience the site catered for, overall content and demographics). Fulfilment of these criteria made the site a suitable candidate for US-based IP address users. Using these standards, retargeting was based on data provided by the third party retargeting company (website details were provided). The retargeting companies service was used in addition to Biogen Idec's US affiliate's advertising agency's own internal proprietary data warehouse.

Biogen Idec confirmed that viewing or being served a Tysabri advertisement on The Telegraph website could only be done via a US IP address due to the US-only campaign specifications. It confirmed that for this retargeting to occur, one must have previously been exposed to a Tysabri advertisement whilst being on a US server or IP address.

Biogen Idec noted out that The Telegraph online, although a UK newspaper, had global readership. Based on information provided by The Telegraph, approximately 23% of the hits to its website in June 2011 were from the US. This constituted the majority (44%) of hits received excluding the UK.

FURTHER INFORMATION FROM THE COMPLAINANT

In response to a request for further information about whether the computer on which the complainant saw the advertisement had a US IP address and whether the complainant or other person using the computer could recall seeing the advertisement previously on a US site the complainant stated that she had no idea and that she had used her home computer. The complainant explained that she had used the UK Google site but did not use the computer for much other than emails and keeping up with the news. The complainant could not think of any website used that would lead her to receiving the advertisement while reading a UK newspaper online. The complainant was British and resided in the UK.

PANEL RULING

The Panel noted that the complainant, a British resident, had seen a US advertisement for Biogen Idec's prescription only medicine Tysabri on the on-line version of The Telegraph. The Panel noted that Clause 22.1 prohibited the promotion of a prescription only medicine to the public. The Code reflected UK and European law in this regard. Clause 22.1 and its supplementary information was silent on matters of nationality.

The Panel noted that the material at issue was a retargeted advertisement placed by Biogen Idec's US affiliate and that Biogen Idec in the UK had no role in the creation or publication of the advertisement. The Panel did not accept the company's submission that the Code was not intended to cover legitimate extra-territorial promotional activities by non-UK entities who were not within the jurisdiction of the Code and whose activities were not intended to be directed or routed to a UK audience under Clause 1.1. The position was not so simple. The Panel noted that it was an established principle under the Code that UK companies were responsible for the acts/omissions of their overseas affiliates that came within the scope of the Code. If it were otherwise, UK companies would be able to rely on such acts and omissions as a means of circumventing the requirements of the Code. Biogen Idec UK was thus responsible for the acts and omissions of its US affiliate that came within the scope of the Code.

The Panel noted that the complainant, a UK resident, had seen an advertisement for a prescription only medicine published on the UK website of a British daily newspaper. The Panel noted Biogen Idec's submission about the newspaper's readership. The Panel considered that the link to the UK was such that the matter came within the scope of the Code.

The Panel noted that the IP address was the unique number assigned to every computer or connection to the internet. Biogen Idec submitted that the complainant must have seen the Tysabri advertisement on a US site before she could be served the same Tysabri advertisement on another site, in this case The Telegraph online. According to Biogen Idec the complainant would have had a US IP address or server.

The Panel noted that the complainant did not know what her IP address was. Nonetheless, irrespective of her IP address, she had seen a US advertisement for a prescription only medicine on a UK website and provided a screenshot copy of it.

The Panel noted that retargeting was a US initiative. The retargeting service and data was provided by a

third party; a link to its website was provided although Biogen Idec had not highlighted any particular part of it. According to the third party's website its service allowed companies to automatically target content and messages with the highest degree of data depth available based on user IP addresses. It also referred to data at postcode level. The page on geo-targeted online advertising explained that advertisers could geo-target to city level (IP city) worldwide and incorporate other parameters. It was not entirely clear which element of the service had actually been used by Biogen Idec's US affiliate. In addition, the US affiliate's advertising agency's internal proprietary data was used for retargeting. The Panel had no information about the retargeting parameters used by the affiliate's advertising agency. Biogen Idec's response only referred to a US IP address or a US server. It did not appear that retargeting had taken place at any greater depth.

The Panel queried whether retargeting at the level used by Biogen Idec's US affiliate was sufficiently sophisticated to ensure compliance with the Code which prohibited the advertising of prescription only medicines to the public.

The Panel also queried whether, irrespective of its comments above about retargeting, The Telegraph online was an appropriate forum on which to re-serve a targeted US advertisement for a prescription only medicine. Both its readership and content were relevant. The Telegraph was a British newspaper which published UK and global news from a UK perspective. The Panel noted Biogen Idec's submission about its global readership and percentage of US hits. The Panel noted that both within Western Europe and globally in June 2011 the largest single absolute number of hits to the UK website was from the UK. In June 2011 48% of hits were from the UK and 23% were from the US. The Panel noted Biogen Idec's submission that the retargeting criteria that qualified The Telegraph as a suitable site for US based IP address users were the type of audience the site catered for, overall content and demographics.

The complainant, a UK resident, had seen a US advertisement for a prescription only medicine on a website for a UK daily newspaper. The complainant did not know her IP address. The Panel noted its comments above about retargeting. Overall the Panel considered that retargeting did not appear to be sufficiently sophisticated to ensure compliance with the Code. The Panel considered on balance that a user's IP address or location of the user's server was not a sufficiently precise surrogate for the user's status in the UK so as to ensure compliance with Clause 22.1 which prohibited the promotion of a prescription only medicine to the public. The Panel considered that irrespective of whether the complainant had a UK or US IP address, the publication of the retargeted US Tysabri advertisement in The Telegraph on line as seen by the complainant constituted promotion of a prescription only medicine to the public. A breach of Clause 22.1 was ruled.

The Panel noted its ruling of a breach of the Code above. A prescription only medicine had been promoted to the public. The Panel queried whether sufficient regard had been paid by the US affiliate to compliance with overseas laws and regulations. High standards had not been maintained. A breach of Clause 9.1 was ruled.

Overall, the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure. Some attempt, albeit unsatisfactory, had been made to ensure a link to a US audience. No breach of Clause 2 was ruled.

APPEAL BY BIOGEN IDEC

Biogen Idec strongly disagreed with the ruling of a breach of Clause 9.1 as both it and its US affiliate had maintained standards commensurate with industry best practice, in both jurisdictions. Specifically, Biogen Idec disagreed with the Panel's assertion that a user's IP address or server location was not a sufficiently precise surrogate for the user's status in the UK. On the contrary, that IP address was the only practicable means by which targeting to an extra-jurisdictional audience could be viably prevented. By targeting US IP addresses only, the US affiliate had at all times maintained high standards and had also respected applicable law and codes with respect to all ex-US jurisdictions.

Biogen Idec disagreed that there had been any breach, including an inadvertent breach, of Clause 22.1. For the reasons stated above, it did not believe that the possibility of accessing, via a US IP address, a legitimate US advertisement, targeted at the US public by a US legal entity constituted a lapse in standards that provoked the mischief that Clause 22.1 sought to address. Notwithstanding requests, Biogen Idec submitted that it been provided with insufficient evidence to confirm that the complainant viewed the advertisement in question from a non-US IP address and, despite repeated efforts, Biogen Idec had been unable to access the advertisement in question (or any prescription only medicine advertisement banner) from such an IP address.

Clause 9.1

With regard to the ruling of a breach of Clause 9.1, Biogen Idec noted that the Panel stated that a prescription only medicine had been advertised to the public. The Panel queried whether sufficient regard had been paid by the US affiliate to comply with overseas laws and regulations. Biogen Idec strongly disagreed with the Panel's assertion that high standards had not been maintained for the following reasons:

- As described above, targeting of advertisements was based solely on US IP addresses. This was a

standard industry practice. The target audience was newspaper readers in the US. The US pharmaceutical industry used retargeting methodology ie targeting US IP address websites after a consumer had voluntarily accessed a product advertisement online via a US IP address. Newspapers offered high quality US audiences who wished to be informed including a wish to be informed of relevant information regarding treatment choices.

Biogen Idec submitted that of the 3,223 websites included in the 2011 media buy related to the Tysabri advertisement banner, 80 could be classified as 'newspaper sites' of which four were UK sites. The UK sites were part of a standard media buy package. They were not pre-selected. Biogen Idec's US affiliate was not incentivised to target non-US patients, nor would it be inclined or motivated to do so. All of the US affiliate's promotional effort was focused on the US and Puerto Rico.

Biogen Idec submitted that 23% of the website hits to The Telegraph in June 2011 were in the US (or via a US IP address) and over 50% of the hits were via non-UK IP addresses. Biogen Idec agreed that 48% of the readers were based in the UK, however given that the advertisement in question was targeted via US IP addresses only, the UK readers of the on-line newspaper were not able to view the Tysabri advertisement banner. Therefore Biogen Idec did not believe that the location of a website, its readership or its country of origin was ultimately a deciding factor as to whether its exposure to a member of the public in the UK resulted in a breach of the Clause 9.1 (or in turn, Clause 22.1). Biogen Idec did not believe that UK readers accessing the website from home in the UK using their standard UK IP addresses would be subject to unsolicited direct-to-consumer advertising of a prescription medicine. Despite repeated efforts to access such advertising via UK home internet accounts (ie via UK IP addresses), Biogen Idec had not found any evidence to the contrary in relation to Tysabri advertisements, or advertisements for any other company. Biogen Idec provided examples of The Telegraph website accessed in August from the UK via a US IP address and accessed in August from the UK using a UK IP address. Both examples displayed The Telegraph website page subject to the complaint but different advertisements clearly targeted to US and UK audiences respectively.

Biogen Idec submitted a memorandum provided by its US affiliate from the internet advertising vendor which confirmed (with 99.9% certainty) that the complainant would have viewed the advertisement via a US IP address. In addition, Biogen Idec had further corroborative confirmation from The Telegraph that targeting was based on IP address, thus UK-targeted advertisements could only be seen from UK IP addresses, and US-targeted advertisements could only be seen from US IP addresses.

Biogen Idec submitted that the key determining factor was whether the advertisement was directed to a UK resident via a UK IP address. Unless it could be proven otherwise, Biogen Idec and its US affiliate had met high standards by ensuring that targeting was based on US IP addresses only.

Clause 22.1

With regard to the alleged promotion of a prescription only medicine to the public, Biogen Idec noted that the Panel stated that, on balance, a user's IP address or location or the user's server was not a sufficiently precise surrogate for the user's status in the UK so as to ensure compliance with Clause 22.1, which prohibited the promotion of prescription only medicines to the public. The Panel considered that irrespective of whether the complainant had a UK or US IP address, the publication of a retargeted US Tysabri advertisement in The Telegraph on line as seen by the complainant was in breach of Clause 22.1.

In response, Biogen Idec raised the following:

- The supplementary information to Clause 22.1 was silent on matters of nationality. As an industry, it would be reasonably expected that home internet users in the UK accessed the internet via UK IP addresses. There might be exceptions such as users accessing the internet through non-UK networks or IP addresses, such as company networks for some US-based organisations. In those circumstances, individuals had made an informed choice to access the internet though such channels. A similar analogy could be made for UK residents exposed to a US direct-to-consumer television advertisement, whether they viewed such advertisement in the US or via other electronic media or platforms in the UK. They would have made an informed choice to be subject to such material via a medium which was clearly routed to a US media audience.

- Biogen Idec had previously asked for confirmation that the complainant viewed the website page from a UK server or IP address. None was provided. The complainant also stated she had no idea whether she, or any other users of her home computer, recalled viewing the advertisement previously on a US website. Given previous submissions regarding firstly accessing a US promotional product website, and subsequently being retargeted to view the advertisement when viewing other websites accessed via US IP addresses, Biogen Idec submitted that its questions had not been answered appropriately. It was unusual for a breach of the Code to be ruled when Biogen Idec could not corroborate or confirm the allegation in question.

Biogen Idec noted that the URL was not visible on the poor quality image of the screenshot which was provided by the complainant. It did not appear to be a *bona fide* screenshot of the screen image. In addition, the URL in question (www.telegraph.co.uk)

was not visible on the screen. Biogen Idec found it highly unusual that this evidence was not captured when the complaint was submitted to corroborate the claim that the advertisement appeared on the website in question (eg via electronic screenshot), and that verbal assurances were provided instead. Biogen Idec noted that in the example screenshot of the relevant website page in question, which was accessed via a US IP address the website URL was clearly visible. Biogen Idec could only assume that the image sent by the complainant was not in fact a complete screenshot of the image displayed on the screen. Although Biogen Idec believed that access to the internet via a US IP address was an appropriate means of directing prescription only medicine advertising to an appropriate audience, no evidence was submitted to prove that the complainant accessed the UK website which was subject to the claim (www.telegraph.co.uk).

Given the poor quality of the image submitted, the absence of proof regarding the legitimacy of the URL accessed, and insufficient level of detail provided in response to its questions, Biogen Idec submitted that insufficient evidence had been submitted to support the assertion that it or its US affiliate had breached Clause 22.1.

Industry Practice

Biogen Idec submitted that IP addresses had been used to target and to exclude users for more than a decade, and that the use of IP addresses for that purpose was the industry standard form of geo-targeting. Biogen Idec provided two prescription only medicine advertisements viewed from the UK, by a UK resident, accessed from a US IP address from publicly available websites. Both of these products were prescription only medicines in the UK, but, as with the Tysabri advertisement at issue, clearly intended for a US consumer audience (reference to US consumer Important Safety Information was clear), and routed through a US IP address. Unless otherwise proven/demonstrated, Biogen Idec submitted that this was the case for the Tysabri advertisement in question. Additional examples of a similar nature for other products could also be provided. Biogen Idec did not believe any of these manufacturers were targeting UK residents. Moreover, they were using US IP addresses as their firewall to ensure that such material was not targeted at UK residents. None of the examples were in breach of the Code.

Biogen Idec submitted that if evidence could be provided that the advertisement was accessed via a UK IP address (something Biogen Idec had not been unable to achieve and the chances of which were extremely improbable), the only means by which the complainant would not have been able to see the advertisement was if all co.uk websites had been blocked for retargeting.

However, Biogen Idec submitted that if the complainant had accessed a .com website, she might have been re-served the advertisement (ie a user being served an advertisement banner after voluntarily accessing the advertisement on a US website). Clearly, there were numerous, globally accessible .com websites. The only 100% effective means by which a UK resident could not be re-served the advertisement (regardless of IP address) would be if all websites were blocked for retargeting. Blocking the retargeting to .com websites would result in a significant global impact including a significant impact on prescription medicine advertising in the US where the practice was legal.

In order to have seen the Tysabri banner advertisement in question on any website, the recipient must have initially viewed the advertisement via a US IP address, and then re-served the advertisement (in this case, via telegraph.co.uk) also via a US IP address.

Summary

Biogen Idec strongly believed that targeting via IP address was a robust, accepted, responsible, and practicable industry standard, and an effective means by which a US consumer might be subject to direct-to-consumer advertising without infringement of overseas laws and codes. The fact that a member of the UK public was able to access a Tysabri advertisement via a US IP address was not evidence of either failure to maintain standards or an intentional or inadvertent wrongful advertisement to the public. There was insufficient evidence to confirm that the advertisement in question was not accessed via a US IP address.

COMMENTS FROM THE COMPLAINANT

The complainant noted that it was a shame that the advertisement appeared through a UK internet service provider's connection.

APPEAL BOARD RULING

The Appeal Board noted from Biogen Idec that advertisement retargeting ie re-serving an internet user with an advertisement on a different website from that on which he/she had viewed it before, was based on geographic-specific IP addresses. This type of retargeting was standard for the internet as a whole. This was how Biogen Idec US could retarget its advertisements only to those with a US IP address. The Telegraph website, telegraph.co.uk, (when accessed via a US IP address) was included in the retargeting package purchased by Biogen Idec US.

The Appeal Board noted Biogen Idec's view that the Internet Service Provider (ISP), the means by which access to the internet was provided, could not determine the user's geographical location. It was possible to connect to a US IP address via a UK ISP.

The Appeal Board noted Biogen Idec's submission that, with 99.9% certainty, to have seen the advertisement at issue the complainant would have

had to have first seen it on the Tysabri.com website via a US IP address. Only then would the complainant have been retargeted with the advertisement on The Telegraph website when this was also accessed via the same US IP address.

There appeared to be inconsistencies between the written submissions and the presentation as to whether the reader had to visit a specific US site, previously responded to a US Tysabri advertisement or merely have seen a US Tysabri advertisement.

At the appeal hearing Biogen Idec's representatives stated that the advertisement in question could only be viewed if the reader's IP address had been 'retargeted'. In order for this to happen two conditions had to be met: firstly the reader must voluntarily have accessed a US Tysabri website via a US IP address and secondly the reader must have then subsequently viewed another website using the same US IP address. The slide stated that thus the advertisement could only be seen if the reader had viewed at least two US websites (including specifically the Tysabri US website) using a US IP address. This was described as a core element of Biogen Idec's US 'media buy' package for this activity.

The Appeal Board further noted from Biogen Idec's submission that it would expect the majority of internet users in the UK to have a UK IP address. Exceptions to that might include those who worked for a US company and accessed the internet via their employer's internet connection or those who had installed specialist software to provide a US IP address even though they accessed the internet via a UK internet provider. The complainant had not stated that either of these applied.

The Appeal Board considered that it was confusing that an advertisement for a prescription only medicine was linked to a .co.uk website as it would appear to some readers (albeit those with US IP addresses) that the advertisement was a part of the .co.uk website when in fact that was not so.

The Appeal Board considered that advertising prescription only medicines to the public was a serious matter. However the complainant had the burden of proving her complaint on the balance of probabilities and in that regard had provided limited information and had not confirmed her IP address.

The Appeal Board considered that the complainant had not established her case on the balance of probabilities and thus ruled no breach of Clause 22.1. The Appeal Board did not consider that Biogen Idec had failed to maintain high standards. No breach of Clause 9.1 was ruled. The appeal on both points was successful.

Complaint received	**11 July 2011**
Case completed	**12 October 2011**

ANONYMOUS v ROCHE

Conduct of representative

An anonymous, non-contactable NHS employee complained about the promotion of Pegasys (peginterferon alfa-2a), a treatment for hepatitis C marketed by Roche. The complainant was particularly concerned about the actions of a representative who was married to the nurse specialist responsible for choosing the treatment for hepatitis C in a large teaching hospital.

The complainant alleged that as a result of the sales performance of Pegasys the couple had benefited from large cash bonuses and won a trip to the Caribbean. Further income was derived from Roche in terms of speaker fees for the representative's wife.

The complainant alleged that Roche had fully encouraged this appalling breach of ethics.

The detailed response from Roche is given below.

The Panel noted that the complainant was anonymous and non-contactable. General allegations about a representative's conduct were difficult to resolve. A complainant had the burden of proving their complaint on the balance of probabilities. The weight to be attached to evidence might be adversely affected if the source was anonymous. In this case very few details had been provided and there was no way to ask the complainant for more information.

The Panel noted Roche's submission that the representative in question had declared the potential conflict of interest to Roche in line with company policy.

The Panel noted Roche's statement that the representative's wife was considered to be one of the UK's most established and accomplished hepatitis C clinical nurse specialists but that she did not actively prescribe in her current role and nor was she able to influence patient medication.

The Panel noted Roche's submission that when the representative's wife moved to a teaching hospital in the representative's territory, the representative informed his line manager. Roche submitted that it was agreed that as Pegasys was already the treatment of choice at the hospital, there was essentially no conflict of interest. The Panel noted from Roche's submission that the representative's wife also spoke to her line manager who did not think there was a conflict of interest because the choice of hepatitis C treatment was not within her remit.

The Panel noted that since 2009 the representative's wife had presented at four Roche meetings. Given her own professional standing, it did not seem unreasonable that Roche should ask her to speak at meetings on its behalf. There was a contract in place and the speaker fees did not appear unreasonable. No breach of the Code was ruled.

The Panel noted the salary and incentive payments received by the representative for 2008-2010. There was a significant increase in the incentive payment received for 2010 which seemed to be proportional to the increase in sales of Pegasys at the hospital where his wife worked.

Roche submitted that the Caribbean trip was an award that recognised performance vs target for 2010, performance management plus demonstration of the Roche values. The Panel noted that the representative's wife accompanied him on this trip as his guest.

The Panel noted that it was inevitable that there would be instances when a representative was married to a health professional. Companies should be mindful of the external perception particularly if the husband and wife had professional interests and/or influence in the same therapeutic area. The Panel noted that the complainant had the burden of proving their complaint on the balance of probabilities. The Panel had some concerns about the conflict of interest and the impression created by the arrangements but noted Roche's submission that both parties had been transparent with their line managers about the situation. The Panel could understand the complainant's concerns but did not consider that he or she had provided evidence to show that on the balance of probabilities the representative or the company had acted contrary to the requirements of the Code. The representative had not failed to maintain high standards, and no breach of the Code was ruled in that regard. In the Panel's view the 2010 incentive payment was on the limits of acceptability. On balance the Panel did not consider that it constituted an undue proportion of the representative's basic salary, and no breach of the Code was ruled. The Panel consequently considered that high standards had been maintained and ruled no breach of the Code in that regard. The Panel noted its rulings above and ruled no breach of Clause 2.

An anonymous, non-contactable NHS employee complained about the promotion of Pegasys (peginterferon alfa-2a) by Roche, in particular the

actions of a representative.

Pegasys was indicated, *inter alia*, for the treatment of chronic hepatitis C in adult patients who were positive for serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV.

COMPLAINT

The complainant noted that the representative in question was married to the nurse specialist responsible for choosing the treatment for hepatitis C in a large teaching hospital that was on the representative's territory. Roche was well aware of this conflict of interest and seemed to encourage it.

The representative and his wife would have benefited from high levels of cash bonus due to sales performance of Pegasys, and the couple had also won a trip to the Caribbean as a reward for sales of the product. They had derived further income from Roche in terms of honoraria for talks that the representative's wife gave to other nurses.

The complainant alleged that Roche had fully encouraged this situation which the complainant saw as an appalling breach of ethics.

When writing to Roche the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2, 15.7 and 20.1.

RESPONSE

Roche stated that it took the allegations very seriously. Representatives were aware of the need to maintain professional relationships between themselves and the health professionals and appropriate administrative staff on whom they called. Roche recognised that in line with the Code, its representatives must not be paid an undue proportion of salary proportional to sales of medicines and all of its incentive programmes were configured to encourage and reward a high standard of behaviour in business.

Roche submitted that although the representative's wife was one of the UK's most established and accomplished hepatitis C clinical nurse specialists (CNS), and since January 2010 had been a qualified nurse practitioner, she did not actively prescribe in her current role. The clinical decision to use Pegasys at the hospital in question was made before 2007, before the representative or his wife worked at this account. A professor, along with two of his colleagues, had very strong clinical buy in for Pegasys, based on its clinical outcome data and personal experience.

The hospital did not have a treatment protocol as such and each clinician chose the most appropriate treatment for their patients; the consensus for hepatitis C was Pegasys. The representative's wife did not have a role to play in treatment selection *per se*.

The complaint was based on the allegation that the representative's wife was responsible for treatment choice and therefore there was an alleged conflict of interest with her husband promoting Pegasys in the department in which she worked. As the premise on which the complaint was based was false, it was clear that there could be no breach found in this matter. High standards and representatives' high standards were met in this regard and so the alleged breaches of Clauses 9.1 and 15.2 were refuted.

The representative had twice been so employed by Roche with an intervening period in a head office role. He currently worked in the field of hepatitis. During each of the periods that the representative had been in the field his wife had worked at a hospital that was part of his territory. On the first occasion the representative told the Roche business unit manager about the potential conflict of interest. The situation was fully explored but as clinicians and not CNSs decided on product use it was concluded that there was no conflict of interest. Some time after his return to the field, the representative's wife took up a position as hepatitis C CNS at the hospital now in question which, again, was on the representative's territory. The representative told his line manager about the situation and as above because of the role of the clinician in deciding treatment options it was concluded that there was no conflict of interest. There had never been any indication or direction to use personal relationships improperly at Roche. High standards and representatives' high standards were met and in this regard the allegation of a breach of Clauses 9.1 and 15.2 was refuted.

Whilst the representative received bonus under the Infield Incentive Scheme, Roche noted that in addition to sales performance this incentive scheme recognised overall company performance and a number of indicators to demonstrate sound and ethical business behaviour. The bonus paid, due to sales performance, was not an undue proportion of total salary. A copy of the Infield Incentive Scheme was provided, which Roche submitted showed that payments made proportional to the sales of medicine did not constitute an undue proportion of remuneration and in this regard the allegation of a breach of Clause 15.7 was refuted.

The Platinum Reward Trip to which the complainant referred was an award that recognised performance vs target, performance management, which included primary responsibilities and goals, plus demonstration of the Roche values of passion, integrity and courage. It did not reward unethical behaviour or encourage activity that would breach the Code. The award was made to individuals at Roche who under the system referred to by the complainant would have been eligible to have a guest accompany them. A copy of the Platinum Club Rule Book was provided. In Roche's view, the basis of the reward trip complied with Clause 15.7 and therefore Roche refuted the allegation of a breach in this regard.

Roche engaged with health professionals and appropriate administrative staff in accordance with Clause 20 of the Code. The representative's wife had been engaged by Roche on a few occasions due to her academic standing and experience; she was probably considered to be one of the UK's top three hepatitis C CNSs. Roche's view that she had the necessary expertise in accordance with Clause 20.1 was corroborated by the fact that two other pharmaceutical companies had proactively used her expertise. In that regard the allegation of a breach of Clause 20.1 was refuted.

Roche stated that the above showed that it and its representative had not undertaken any unethical activity. In Roche's view, the representative had conducted himself professionally in accordance with both the letter and spirit of the Code. Roche had investigated all activity in relation to this complaint and had established that these had been carried out in accordance with the Code. Roche therefore refuted the complainant's allegations and associated breaches of Clauses 2, 9.1, 15.2, 15.7 and 20.1. Roche took all accusations seriously and trusted its response addressed all the concerns expressed.

Following a request for further information, Roche confirmed that the Roche Group Code of Conduct clearly expressed the company's expectations as an employer and provided employees with practical guidance and links to further information. It included a section on conflicts of interest. The advice given to employees who had a situation that they considered might be an issue was to escalate the concern to their line manager – as the representative in question had done as outlined above. Roche employees also had to sit and pass the Roche Behaviours in Business training module, which contained specific content relating to confidentiality and the expectation of how each employee was expected to conduct themselves at work. The representative in question had completed this training.

Each time the representative's wife had presented on behalf of Roche she had signed a 'Speaker brief and agreement letter' which contained the statement that 'The slides used must include a statement that Roche sponsors the presentation'. She had presented on service delivery at four meetings since 2009 on behalf of Roche and details of the payments were provided together with copies of the agendas. One of the meetings was organized and attended by the representative and took place in December 2010. The title of the meeting was 'Hepatitis C service delivery – Evolving pathways in HCV'. The meeting was chaired by a liver nurse specialist and attended by eleven health professionals.

Roche confirmed that the representative's wife was a qualified nurse practitioner but did not actively prescribe in her current role.

The dates for the Caribbean trip referred to by the complainant were provided.

Roche submitted the basic yearly salary and bonus for the representative for 2008, 2009 and 2010. Roche noted that the increase in sales on the representative's territory in 2010 was driven by positive sales growth at twelve out of seventeen accounts. The hospital at which his wife worked was the second largest contributor to this growth. The Pegasys market share at this hospital was provided. Roche submitted that the increase in sales in 2010 was not due to a switch from a competitor product but due to service expansion/development at the trust. This was not an area in which the representative was involved as this was the remit of the Roche service development specialist.

Roche confirmed that the representative told his line manager that his wife was moving to the hospital in question and hence she would once again be working on his territory. They discussed the fact that as Pegasys was already the treatment choice at the hospital, there was essentially no conflict of interest. The representative also told his manager that, before she accepted the position, his wife had told a professor at the hospital that she was married to the Pegasys hospital sales specialist for Roche. The professor stated that he did not think that there was a conflict of interest because the choice of treatment for their hepatitis C patients was not within the representative's wife's remit.

During the meeting with his line manager, the representative also told him about the conversation he had with the business unit manager when he and his wife had worked at the previous hospital. His wife was a hepatitis CNS at the trust and as clinicians not CNSs decided product use it was concluded that there was no conflict of interest. The line manager discussed with the representative the need for total confidentiality at all times and it was agreed that the representative should always be honest and disclose his relationship with his wife if a situation arose where the representative considered that it was appropriate to do so. The representative told his manager that he and his wife had always been open and transparent about their relationship to all of their internal and external customers when they both worked at the previous hospital, and it would be the intention to do so now that she had moved to the hospital in question. It was again agreed that, as the representative's wife was not in a position to influence patient medication, there was no conflict of interest.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. When a general allegation had been made about a representative's conduct it was difficult to determine precisely what had occurred. As set out in the Constitution and Procedure, a complainant had the burden of proving their complaint on the balance of probabilities. The weight to be attached to evidence might be adversely affected if the source was anonymous. In this case very few details had been provided and there was no way to ask the complainant for more information.

The Panel noted Roche's submission that the representative in question had declared the potential conflict of interest to Roche in line with company policy.

The Panel noted that the representative in question moved to a field-based role that covered the hospital in question in Spring 2008. His wife moved to the position of hepatitis C CNS at the same hospital in late 2009.

The Panel noted Roche's statement that the representative's wife was 'considered to be one of the UK's most established and accomplished hepatitis C CNSs' but that she did not actively prescribe in her current role and nor was she able to influence patient medication.

The Panel noted Roche's submission that when the representative's wife moved to the hospital in question, the representative informed his line manager that she would be working on his territory. Roche had submitted that this was in accordance with its Group Code of Conduct requirements relating to conflicts of interest. Roche submitted that it was agreed that as Pegasys was already the treatment of choice at the hospital, there was essentially no conflict of interest. The Panel noted from Roche's submission that the representative's wife had also talked to a professor at the hospital before accepting a position there, informing him that she was married to the Pegasys hospital sales specialist and the professor did not think there was a conflict of interest because the choice of treatment for hepatitis C patients was not within her remit.

The Panel noted that since 2009 the representative's wife had presented at four Roche meetings and had received speaker fees for these services. One of these meetings was organized and attended by her husband. Roche submitted that the contract the representative's wife signed for each of these meetings contained a statement that 'The slides used must include a statement that Roche sponsors the presentations'. It was not clear to the Panel how the relationship between the representative and his wife was disclosed. Nonetheless, given her own professional standing as a hepatitis C CNS, it did not seem unreasonable that Roche should ask the representative's wife to speak at certain meetings on its behalf. There was a contract in place and the speaker fees did not appear unreasonable. No breach of Clause 20.1 was ruled.

The Panel noted the salary and incentive payments received by the representative for 2008, 2009 and 2010. There was a significant increase in the incentive payment received for 2010. Roche submitted that the increase in sales for the representative's territory in 2010 was driven by sales growth at twelve out of seventeen accounts and the hospital in question was the second largest contributor to this growth. Roche submitted that the increase in sales at the hospital was due to service expansion/development and that this was not an area in which the representative was involved. The Panel noted that the incentive payment for the representative for 2010 did however seem to be proportional to the increase in sales. In the Panel's view, the incentive payment for 2010 was on the limits of acceptability.

Roche submitted that the Caribbean trip was an award that recognised performance vs target for 2010, performance management plus demonstration of the Roche values. The Panel noted that the 'Platinum Club' document provided by Roche stated that nominations for this award were put forward by the line manager based on sales or performance vs target for the qualifying period. The line manager would also include an overview of performance management and demonstration of Roche values, which would also be taken in to consideration. The Panel noted that the representative's wife accompanied him on this trip as his guest.

The Panel noted that the increased incentive payment provided to the representative covered a period that coincided with his wife's move to the hospital in question. In that regard, the Panel questioned the submission that the representative's wife had no influence over prescriptions for hepatitis C patients, given Roche's submission that she was considered to be one of the UK's most established and accomplished hepatitis C CNSs.

The Panel noted that it was inevitable that there would be instances when a representative was married to a health professional. Companies should be mindful of the external perception particularly if the husband and wife had professional interests and/or influence in the same therapeutic area. The Panel noted that the complainant had the burden of proving their complaint on the balance of probabilities. The Panel had some concerns about the conflict of interest and the impression created by the arrangements but noted Roche's submission that both parties had been transparent with their line managers about the situation. The Panel could understand the complainant's concerns, but did not consider that he or she had provided evidence to show that on the balance of probabilities the representative or the company had acted contrary to the requirements of the Code. The representative had not failed to maintain high standards, and no breach of Clause 15.2 was ruled in that regard. In the Panel's view the 2010 incentive payment was on the limits of acceptability. On balance the Panel did not consider that it constituted an undue proportion of the representative's basic salary, and no breach of Clause 15.7 was ruled. The Panel consequently ruled no breach of Clause 9.1. The Panel noted its rulings above and ruled no breach of Clause 2.

Complaint received	**18 July 2011**
Case completed	**17 August 2011**

CASE AUTH/2423/7/11

PHARMACOSMOS v VIFOR PHARMA

Ferinject leavepiece

Pharmacosmos A/S complained about a Ferinject (ferric carboxymaltose solution for injection/ infusion) leavepiece issued by Vifor Pharma UK. Ferinject was indicated for the treatment of iron deficiency when oral preparations were ineffective or could not be used.

The detailed response from Vifor is given below.

The claim 'Mastering the art of iron therapy' appeared as a strapline immediately beneath the product logos on the front page and inside flap of the leavepiece. Pharmacosmos alleged that the claim was that Ferinject was a best-in-class product. As this was non-specific and all-embracing, in the absence of any meaningful best-in-class data, it was misleading in breach of the Code.

The Panel considered that the strapline would be seen as a claim for Ferinject. The Panel noted that to 'master' an art meant to be extremely skilled or accomplished. The Panel considered that the strapline implied that Ferinject had a non-specific special merit compared with other iron therapies. The Panel considered that the claim was misleading in that regard and ruled a breach of the Code.

The claim 'Ferinject reduces time spent in clinics' appeared as a heading to two graphics which detailed administration times based on practical clinic times (including set-up and infusion). The first graphic showed that eight Ferinject patients could be treated in 4 hours compared with one Cosmofer (iron dextran) patient. The second graphic showed that two and a half Ferinject patients could be treated in 75 minutes compared with one Monofer (iron isomaltoside) patient.

Pharmacosmos alleged that the time comparisons were simplistic, without scientific rationale and based solely on the products' summaries of product characteristics (SPCs) with no practical assessment and no direct comparison between the products. There appeared to be an arbitrary 15 minutes administration time added to that quoted in the SPC for actual administration of the product. Only one arbitrary dose (1000mg) was compared instead of a range of doses. Given that Cosmofer and Monofer could be given in higher doses than Ferinject, Pharmacosmos noted that some patients treated in one visit with either Cosmofer or Monofer would require two visits if treated with Ferinject. Patient weight was also an important parameter that had been left out of the comparison. Patients weighing < 67kg would need two visits to receive the 1000mg dose used in the comparison.

The Panel noted that the graphic depicting Ferinject vs iron dextran showed that eight patients could be treated with Ferinject 1000mg in the four hours that it would take to treat one patient with iron dextran 1000mg. The other graphic showed that two and a half Ferinject 1000mg patients could be treated in the time that it took to treat one patient with the same dose of iron isomaltoside. The Panel further noted that both parties acknowledged that there were numerous factors which contributed to the time a patient spent in the clinic. Vifor had attempted to minimise this subjectivity by, *inter alia*, adding what appeared to be an arbitrary 15 minutes set up and tidy up time to the times otherwise calculated from the relevant SPCs. The Panel considered that the depicted absolute differences between the two products were not accurate. A breach of the Code was ruled.

Pharmacosmos A/S complained about the promotion of Ferinject (ferric carboxymaltose solution for injection/infusion) by Vifor Pharma UK Limited. Ferinject was indicated for the treatment of iron deficiency when oral preparations were ineffective or could not be used.

The material at issue was a six-page gatefolded leavepiece (ref 0090A/FER/2011) entitled, 'Benefits of Ferinject in managing iron deficiency anaemia in inflammatory bowel disease (IBD)'. The inside pages appeared to be designed as a single landscape page.

1 Claim 'Mastering the art of iron therapy'

The claim appeared as a strapline immediately beneath the product logos on the front page and inside flap of the leavepiece.

COMPLAINT

Pharmacosmos alleged that the claim was that Ferinject was a best-in-class product. As this was non-specific and all-embracing, in the absence of any meaningful best-in-class data, it was misleading in breach of Clause 7.2.

Pharmacosmos was concerned that Vifor had failed to recognise that this was a promotional claim.

RESPONSE

Vifor submitted that 'Mastering the art of iron

therapy' was an internationally recognized introductory statement which had been used for many years. It was clearly a strapline and not a claim about the product. It did not state or imply any superiority or 'best-in-class' and thus did not require substantiation. It was simply intended to start a discussion between the representative and the health professional on the challenges and 'art' of managing the complexity of iron therapy. Vifor denied a breach of Clause 7.2.

PANEL RULING

The Panel considered that, contrary to Vifor's submission, the strapline 'Mastering the art of iron therapy', in association with the product logo, would be seen as a claim for Ferinject. The Panel noted that to 'master' an art meant to be extremely skilled or accomplished. The Panel did not consider that the strapline implied that Ferinject was a best-in-class product *per se* but it did imply a non-specific special merit for the medicine compared with other iron therapies. The Panel considered that the claim was misleading in that regard and ruled a breach of Clause 7.2.

2 Claim 'Ferinject reduces time spent in clinics'

The claim appeared as a heading to two graphics which provided details of administration times based on practical clinic times (including set-up and infusion). The first compared Ferinject with iron dextran (Cosmofer) and the second compared Ferinject with iron isomaltoside (Monofer). The first graphic showed that eight Ferinject 1000mg patients could be treated in 4 hours compared with one iron dextran 1000mg patient. The second graphic showed that two and a half Ferinject 1000mg patients could be treated in 75 minutes compared with one iron isomaltoside 1000mg patient. Cosmofer and Monofer were Vitaline Pharma UK products (Vitaline Pharma was the UK subsidiary of Pharmacosmos).

COMPLAINT

Pharmacosmos alleged that the claim and accompanying graphics were biased comparisons based on selective parts of the relevant summaries of product characteristics (SPCs) and not head-to-head comparisons based on clinical facts. The comparisons were overly simplistic and considered only one dose and omitted important parameters such as patient weight and maximum doses of the medicines compared. In addition, the SPC data had been arbitrarily altered. Pharmacosmos was not aware of any evidence to support the claim and the supporting graphics and alleged that they were inaccurate, unfair and selective in breach of Clause 7.2.

Pharmacosmos stated that it was unclear whether this was a claim that health professionals spent less time in clinics or that the patient did. However, the claim appeared as a heading above a graphical representation of patients demonstrating that eight Ferinject patients could be seen/treated in the time it took to see/treat a single iron dextran patient or two and a half Ferinject patients when comparing to iron isomaltoside.

The time comparisons were incredibly simplistic and without scientific rationale and based solely on the products' SPCs with no actual assessment of time taken in a practical setting and no direct comparison between the products. The calculation appeared to have arbitrarily added 15 minutes administration time to that quoted in the SPC for actual administration of the product. Only one arbitrary dose (1000mg) was compared instead of a range of doses. The comparisons ignored the fact that Cosmofer and Monofer could be given in higher doses than Ferinject which could have a massive impact on the comparison as some patients handled in one visit with either Cosmofer or Monofer would require two visits if treated with Ferinject. The weight of the patient was also an important parameter that had been left out of the comparison. Patients weighing less than 67kg would need two visits to receive the 1000mg dose used in the comparison.

Pharmacosmos stated that assuming the claim was based on time saved by the health professional, the graphical claim implied that six [*sic*] Ferinject patients could be seen in the time it took to see a single iron dextran patient. This assumed that there was no other clinical or administrative consideration to make in respect of any of the patients; perfect scheduling and that all patients would receive the same dose of product under equivalent conditions. There was no head-to-head assessment in any sense other than the SPC comparison. Again, one arbitrary dose (1000mg) was considered and the fact that Cosmofer could be given in higher doses than Ferinject was ignored.

In inter-company correspondence, Vifor had stated that the claim and supporting graphic represented time spent in clinic by patients. It was difficult to see where the time saving actually occurred as it assumed that the time in the treatment room receiving iron treatment was the only consideration when in reality there were numerous factors to consider in respect of travel time, number of visits, waiting time, concomitant illnesses, time waiting at the pharmacy, etc.

RESPONSE

Vifor submitted that the key issues appeared to be whether the claim 'Ferinject reduces the time spent in clinics' was inaccurate, unfair and selective. Any comparison of intravenous irons would inevitably involve a certain amount of subjectivity as the respective dosage intervals, test dose necessity and observation period requirements varied extensively. This was exacerbated by variations in individual physician and clinic practice with respect to patient set up and appointment times, etc. In this respect, Vifor supported the assertion that *'…* there were numerous factors to consider in respect of travel

time, number of visits, waiting time, concomitant illnesses, time waiting at the pharmacy, etc, etc …'. However, it was clearly impractical to produce a comparison containing all the possible variations in product choice, haemoglobin levels, test dose necessity, observation period, appointment times, patient set up times, patient weight, travel time, number of visits, concomitant illnesses, pharmacy waiting time, etc.

Vifor submitted that it had therefore tried to minimise this subjectivity by referencing the respective SPCs as the most objective reference source available and adding 15 minutes for each product for set up time, individual practice variations, etc. In many ways this mitigated against Ferinject as no test dose was required and so its set up time was usually shorter. Nonetheless, in order to ensure that the comparison was as objective, fair and accurate as possible the standardised value of 15 minutes was used for all products.

The administration times were therefore taken directly from the SPC as stated by the complainant and compared Section 4.2 of the product SPCs at issue. Section 4.2 of the Ferinject SPC stated minimum 15 minutes for 1000g and the diagram showed 30 minutes. As mentioned above, a 15 minute 'set up' and 'tidy up' time was assumed for each patient. The 15 minutes was the same for all products even though the observations for iron dextran were much higher in reality as the product had a test dose requirement before it could be administered. Vifor acknowledged that there would be differences in patients' weights etc but, again, in order to standardise the comparison, the graphic referred to demonstrated 1000g as this was a common dose and was given according to all the relevant SPCs.

Clearly this issue was open to interpretation. However, it was clear that the central claim 'Ferinject reduces the time spent in clinics' could be substantiated as it was administered in 15 minutes whereas all of the comparator products required much longer administration periods. A reasonable person could therefore extrapolate that this would result in a reduction in the time spent in clinics.

Vifor contended that the leavepiece in question was accurate, fair and as objective as possible and was therefore not in breach of Clause 7.2.

PANEL RULING

The Panel noted that the graphic depicting Ferinject vs iron dextran showed that eight patients could be treated with Ferinject 1000mg in the four hours that it would take to treat one patient with iron dextran 1000mg. The other graphic showed that two and a half Ferinject 1000mg patients could be treated in the time that it took to treat one patient with the same dose of iron isomaltoside. The Panel further noted that both parties acknowledged that there were numerous factors which contributed to the time a patient spent in the clinic. Vifor had attempted to minimise this subjectivity by, *inter alia*, adding what appeared to be an arbitrary 15 minutes set up and tidy up time to the times otherwise calculated from the relevant SPCs. The Panel did not agree with Vifor's submission that the addition of this arbitrary figure ensured that the claim was as 'objective, fair and accurate as possible'. In any event the graphics and accompanying text did not refer to the additional 15 minutes.

The Panel noted that the graphics depicted, in absolute terms, the number of patients who could be treated with Ferinject 1000mg in a set time vs the number of patients who could be treated with other intravenous iron preparations. The data to calculate the differences had included the addition of an assumed 15 minutes for set up and tidy up. The Panel considered that the depicted absolute differences between the two products were thus not accurate. A breach of Clause 7.2 was ruled.

Complaint received **27 July 2011**

Case completed **31 August 2011**

CASE AUTH/2430/8/11

GLAXOSMITHKLINE CONSUMER HEALTHCARE v JOHNSON & JOHNSON

Promotion of Nicorette QuickMist

GlaxoSmithKline Consumer Healthcare complained about a mailing for Nicorette QuickMist (nicotine mouthspray) distributed to prescribers by Johnson & Johnson. Nicorette QuickMist was indicated for the relief and/or prevention of craving and nicotine withdrawal symptoms associated with tobacco dependence.

The detailed responses from Johnson & Johnson are given below.

The claim '60 second craving relief' was followed by 'Breakthrough cravings can jeopardise a quit attempt'. GlaxoSmithKline Consumer Healthcare explained that cravings were categorised as withdrawal, background cravings or acute, breakthrough cravings. GlaxoSmithKline Consumer Healthcare alleged that juxtaposing the two claims implied that Nicorette QuickMist would relieve breakthrough cravings in 60 seconds. Although Nicorette QuickMist was licensed to relieve cravings, to presumably include breakthrough cravings, the claim that it would do so in 60 seconds was misleading as the supporting study measured the effect on background cravings, not breakthrough cravings.

The Panel noted that the headline claim for 60 second craving relief was repeated in the first bullet point. The second bullet point read 'Breakthrough cravings can jeopardise a quit attempt'. In the Panel's view prescribers were likely to link the two claims and assume that the cravings relieved in 60 seconds in the first bullet point were breakthrough cravings as referred to in the second.

The Panel noted Johnson & Johnson's submission that there was no universal terminology to describe nicotine cravings. The mailing at issue was distributed to prescribers who, in the Panel's view, might have different understandings of the terms 'breakthrough', 'background', 'provoked', 'cue-induced' and 'situational' when used to describe nicotine cravings. The Panel further noted Johnson & Johnson's submission that breakthrough cravings were not directly linked to the 60 second claim. Given the juxtaposing of the two claims, however, and the lack of a common understanding of terms to describe cravings, the Panel considered that the mailing was misleading as alleged. A breach of the Code was ruled.

GlaxoSmithKline Consumer Healthcare alleged that the claim 'Cost of treatment: £1.23 per day for an average 20 per day smoker, using one spray in place of their normal cigarette' was in breach of the Code. The main message of the mailing was of 60 second craving relief based on a study that used a dose of 2 sprays. The cost claim was clearly based on a dose of 1 spray per cigarette, but as the main thrust of the mailing was about 60 second craving relief which was based on a dose of 2 sprays, GlaxoSmithKline Consumer Healthcare alleged that the cost claim was misleading. Further, the footnote declared that the cost was based on the duo pack, yet the large visual on the mailing was of the single pack.

The Panel noted that the '60 second craving relief' claim was based upon the results of a study in which patients had used two sprays of Nicorette QuickMist instead of smoking a cigarette. The two spray dosing regimen for this study was not made clear in the mailing. The cost claim at issue, however, was based on the use of one spray in place of a cigarette. Further, the mailing featured a photograph of a one dispenser pack (£11.48) but, according to a footnote, the cost claim was based on the duo dispenser pack (£9.25 per dispenser). The Panel thus considered that the claim 'Cost of treatment: £1.23 per day for an average 20 per day smoker, using one spray in place of their normal cigarette' was misleading as alleged. A breach of the Code was ruled.

GlaxoSmithKline Consumer Healthcare complained about a mailing (ref 06458) for Nicorette QuickMist (nicotine mouthspray) distributed to prescribers by Johnson & Johnson Limited. Nicorette QuickMist was indicated for the relief and/or prevention of craving and nicotine withdrawal symptoms associated with tobacco dependence.

1 Claims '60 second craving relief' followed by 'Breakthrough cravings can jeopardise a quit attempt'

The 60 second claim was referenced to 'Data on file 002' and the claim about breakthrough cravings was referenced to Shiffman *et al* (1996).

COMPLAINT

GlaxoSmithKline Consumer Healthcare explained that cravings to smoke were categorised as withdrawal, background cravings or acute, breakthrough cravings. The latter were also referred

to as situational, cue-induced or provoked cravings. Background cravings were thought to result from the physical withdrawal of nicotine from the body and the latter resulted from provocation by cues associated with smoking. Johnson & Johnson knew about these differences and highlighted them in an advertisement (ref 06841, March 2011) which stated 'Background nicotine cravings plus situational cravings are significant factors …'. Johnson & Johnson also recognised in the advertisement that it was these intense, cue-induced cravings that could lead to immediate lapse.

The headline of the mailing at issue referred to 60 second craving relief and that the product 'acts fast'. The first bullet point reiterated this and claimed that 'Nicorette QuickMist, in an open label study, was clinically proven to relieve cravings in just 60 seconds'. The second bullet point stated that 'Breakthrough cravings can jeopardise a quit attempt'. Although this claim was true, juxtaposing the two claims implied that Nicorette QuickMist would relieve these breakthrough cravings in just 60 seconds. Although Nicorette QuickMist was licensed to relieve cravings, to presumably include breakthrough cravings, it was the claim that it would do so in 60 seconds that was in dispute as the study used to support this claim measured the effect on background cravings, not breakthrough cravings. The methods reported to evaluate the effect of Nicorette QuickMist on cravings showed that subjects were deprived of nicotine for 5 hours (after self-reported overnight abstinence) and were not given any cues to trigger a breakthrough craving before they were given the study medicine. Thus the study measured the effect of the interventions on background craving, not of breakthrough/cue-provoked craving. In inter-company correspondence, Johnson & Johnson claimed that the study was similar to Durcan *et al* (2004) which specifically looked at cue-provoked craving but this was not so. Participants in Durcan *et al* had to be abstinent for a number of hours and were then asked to unwrap a pack of their usual cigarettes; remove, light and hold the cigarette (without placing it in the mouth) for one minute. After extinguishing the cigarette, post-provocation craving was assessed and then the treatments were administered and the effects on this craving measured. It was this cue-provoked craving that was then relieved by using NiQuitin 4mg lozenge. This was substantially different from the methodology used in the Nicorette QuickMist study which only involved abstinence from smoking for a number of hours, and did not involve any further triggering of a cue-provoked/breakthrough craving.

The direct implication of juxtaposing the claims that Nicorette QuickMist relieved cravings in just 60 seconds and that breakthrough cravings could jeopardise a quit attempt was that Nicorette QuickMist had been shown to relieve breakthrough cravings in 60 seconds. This was not so. GlaxoSmithKline alleged that the mailing was thus misleading in breach of Clause 7.2.

RESPONSE

Johnson & Johnson noted that the mailing included a headline to show the fast-acting nature of Nicorette QuickMist; this was followed by a number of bullet points which outlined the benefits and attributes of the medicine itself. The bullet point at issue, 'Breakthrough cravings can jeopardise a quit attempt' was one of a number of bullet points in the mailing.

Johnson & Johnson noted the complainant's concern regarding the differentiation between background and breakthrough cravings and that juxtaposing the two claims 'Nicorette QuickMist, in an open label study, was clinically proven to relieve cravings in just 60 seconds' and 'Breakthrough cravings can jeopardise a quit attempt' implied that Nicorette QuickMist had been shown to relieve breakthrough cravings in 60 seconds.

Johnson & Johnson noted that GlaxoSmithKline Consumer Healthcare categorised cravings into two types; background and breakthrough. However, Johnson & Johnson submitted that the situation was more complex than that and there was no universal or standard terminology to describe nicotine cravings. All cravings were part of the nicotine withdrawal syndrome and could be referred to in terms of how they were induced, their severity, duration and whether they occurred despite a background level of nicotine.

Johnson & Johnson submitted that 'breakthrough cravings' was often used to describe cravings which occurred despite a level of background nicotine already being present. GlaxoSmithKline Consumer Healthcare used this term itself at recent symposia. It was not necessarily the case however, that breakthrough cravings were the same as cue-induced or situational cravings, as it might not be a cue, situation or provocation which resulted in the craving.

The Nicorette QuickMist summary of product characteristics (SPC) stated that the product was indicated to relieve and/or prevent cravings and nicotine withdrawal symptoms associated with tobacco dependence. As such, the SPC did not specify or categorise the types of cravings that Nicorette QuickMist should be used to relieve. Therefore, it was entirely reasonable to suggest that Nicorette QuickMist could be used to relieve any type of cravings that a smoker might experience.

The Nicorette QuickMist craving study (Hansson *et al* 2011) was a well designed study which used a well established model to provoke cravings in the study group. The study involved provoking cravings after 5 hours of witnessed abstinence.

Johnson & Johnson submitted that the concept of using provocation as a model for cravings was widely used and there were a number of approaches to provoking cravings in a study of this type. Both the Nicorette QuickMist craving study

and Durcan *et al* used a model of provoked cravings. Johnson & Johnson submitted that regardless of how provocation was accomplished, provoking cravings and the concept of using provoked cravings in a clinical study as a model for cravings was widely accepted.

The advertisement referred to by GlaxoSmithKline Consumer Healthcare (ref 06841), was an advertorial which separated out cravings. However, the term 'breakthrough cravings' had not been used. Any type of nicotine craving could lead to lapse or indeed relapse, regardless of the cause of the craving.

In summary, Johnson & Johnson stated that the claim 'Breakthrough cravings can jeopardise a quit attempt' was one bullet point within the mailing and was not directly linked to the '60 second craving relief' claim which appeared in the headline. The company believed that the use of 'breakthrough cravings' in the context of this mailing was justified and was not misleading, and disagreed with GlaxoSmithKline Consumer Healthcare that the term 'breakthrough cravings' only referred to 'acute, cue-provoked cravings'. Johnson & Johnson denied a breach of Clause 7.2.

In response to a request for further information, Johnson & Johnson submitted that Hansson *et al* was the published outcome of 'Data on file 002' which was cited in the mailing itself. Although the company was aware of the study and the key outcomes, it did not see the final Hansson *et al* publication until after it was published on 16 February 2011 ie a week after the mailing was certified.

PANEL RULING

The Panel noted that the headline claim for 60 second craving relief was repeated in the first bullet point, 'Nicorette QuickMist, in an open label study, was clinically proven to relieve cravings in just 60 seconds'. The headline claim and first bullet point were referenced to 'Data on file 002', a study in which smokers were given two sprays of Nicorette QuickMist, a 2mg NiQuitin Lozenge or a 4mg NiQuitin Lozenge after 5 hours of witnessed abstinence. Urges to smoke were scored on a 100mm visual analogue scale in the first minute post-administration. The mean differences between mouth spray and either strength of the lozenges were statistically significant ($p<0.001$).

The Panel noted that the '60 second' bullet point was followed by the second bullet point which read 'Breakthrough cravings can jeopardise a quit attempt'. In the Panel's view prescribers were likely to link the two claims and assume that the cravings relieved in 60 seconds in the first bullet point were breakthrough cravings as referred to in the second.

The Panel noted Johnson & Johnson's submission that there was no universal or standard terminology to describe nicotine cravings. The mailing at issue was distributed to prescribers who, in the Panel's view, might have different understandings of the terms 'breakthrough', 'background', 'provoked', 'cue-induced' and 'situational' when used to describe nicotine cravings. The Panel further noted Johnson & Johnson's submission that breakthrough cravings were not directly linked to the '60 second craving relief claim'. Given the juxtaposing of the two claims, however, and the lack of a common understanding of terms to describe cravings, the Panel considered that the mailing was misleading as alleged. A breach of Clause 7.2 was ruled.

2 Claim 'Cost of treatment: £1.23 per day for an average 20 per day smoker, using one spray in place of their normal cigarette**

****Based on the NHS cost of the duo pack'**

COMPLAINT

GlaxoSmithKline Consumer Healthcare stated that the main message of the mailing was the 60 second craving relief claim. It appeared as the headline, the first bullet point and as one of the key take-home points. The study that generated the 60 second relief claim used a dose of 2 sprays, but this was not stated in the mailing. The cost claim was clearly based on a dosing of 1 spray per cigarette, but as the main thrust of the mailer was about 60 second craving relief and this was based on a dose of 2 sprays, GlaxoSmithKline Consumer Healthcare alleged that this was misleading. Similarly, the footnote declared the cost was based on using the duo pack, yet the large visual on the mailer was of a single pack.

In inter-company correspondence Johnson & Johnson stated that it had been careful to include all relevant information in the bullet point 'Cost of treatment: £1.23 per day for an average 20 per day smoker, using one spray in place of their normal cigarette**', '**Based on the NHS cost of the duo pack'.

GlaxoSmithKline Consumer Healthcare stated that Johnson & Johnson's defence of the cost claim could not be seen in isolation from the 60 second claim as it was part of the same mailing, with the 60 second claim being the most prominent message. Readers would assume that the cost was thus based on the same dosing schedule unless stated otherwise. GlaxoSmithKline Consumer Healthcare therefore alleged that the claim was misleading in breach of Clause 7.2.

RESPONSE

Johnson & Johnson stated that it deliberately sought to ensure that the claim included all relevant information, both to avoid confusion and ensure that this was made absolutely clear to prescribers. The claim 'Cost of treatment: £1.23 per day for an average 20 per day smoker, using one spray in place of their normal cigarette**' included some

additional information, '**Based on the NHS cost of the duo pack' to provide prescribers with all the relevant information, to allow them to make a fully informed decision about the product.

Johnson & Johnson noted that an additional bullet had also been included within the mailer to highlight the dosing schedule of Nicorette QuickMist. The bullet 'Flexible dosing regimen: 1 or 2 sprays to be used when cigarettes would have normally been smoked or if cravings emerge' made it clear to the reader that the dosing could be one or two sprays. Furthermore, the dosing of the product and the prices for both the 1 and 2 dispenser packs were included within the prescribing information.

Johnson & Johnson considered that it was clear within the body of the claim that the cost was based on an average 20 per day smoker, using one spray in place of their normal cigarette. The wording could not have been clearer and Johnson & Johnson failed to understand how the claim could mislead. The company denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim for '60 second craving relief' which featured in the headlines on the front and back of the mailing and in the first bullet point on the front page, was based upon the results of a study in which patients had used two sprays of Nicorette QuickMist instead of smoking a cigarette. The two spray dosing regimen for this study was not made clear in the mailing. The cost claim at issue, however, was based on the use of one spray in place of smoking a cigarette.

The mailing featured the photograph of a one dispenser pack which had an NHS cost of £11.48; the cost claim at issue was based on the cost of the duo dispenser pack which had an NHS cost of £18.50 ie £9.25 per dispenser.

The Panel noted that if the cost claim had been based on the use of a two spray dose to replace each cigarette, from a one dispenser pack, the daily cost of treatment would be £3.06.

The Panel thus considered that the claim 'Cost of treatment: £1.23 per day for an average 20 per day smoker, using one spray in place of their normal cigarette' was misleading. Although a footnote read 'Based on the NHS cost of the duo pack' the Panel noted that claims must be capable of standing alone and in general should not be qualified by the use of footnotes. In the Panel's view, readers would assume that the daily cost of Nicorette QuickMist treatment was based upon the use of the one dispenser pack illustrated.

Given the clinical claims in the mailing and the photograph of the one dispenser pack, the Panel considered that the claim at issue was misleading as alleged. A breach of Clause 7.2 was ruled.

Complaint received **8 August 2011**

Case completed **15 September 2011**

GENERAL PRACTITIONER v LILLY

Legibility of prescribing information

A general practitioner complained that the prescribing information on an advertisement for Bydureon (exenatide) was incredibly difficult to read.

The detailed response from Lilly is given below.

The Panel noted that the Code required prescribing information to be given in a clear and legible manner. Relevant supplementary information listed a number of factors which would help achieve clarity. The Panel considered that the prescribing information was on the limits of acceptability with regard to the contrast between text and background. However, on the whole, the Panel considered that, although not easy to read, the prescribing information did not fail to comply with the Code and no breach was ruled. The Panel noted Lilly's intention to change the combination of font, colour and background in future material.

A general practitioner complained about a Bydureon (exenatide) outsert that was attached to the July/August 2011 edition of Practical Diabetes. Bydureon, marketed by Eli Lilly and Company Limited, was an oral add-on therapy indicated in type 2 diabetes in adults who had not otherwise achieved adequate glycaemic control on maximally tolerated doses of other oral anti-diabetic agents.

COMPLAINT

The complainant alleged that the prescribing information was incredibly difficult to read and in his opinion contravened Clause 4.1 of the Code, which stated that 'a clear style of type should be used' and 'dark print and light background is preferable'.

The complainant stated that, ironically, the same journal had contained an article entitled 'Consumers find food labels confusing and too small to read'; it appeared the pharmaceutical industry and the food industry had a lot in common.

RESPONSE

Lilly considered that the prescribing information met the requirements of the Code; the text was of an appropriate height, spacing, style and legibility and thus the prescribing information had been provided in a clear and legible manner. Lilly denied a breach of Clause 4.1.

Notwithstanding the above, Lilly submitted that it would change the combination of font, colour and background of the prescribing information in future materials.

PANEL RULING

The Panel noted that Clause 4.1 required that prescribing information be given in a clear and legible manner. The supplementary information to Clause 4.1, Legibility of Prescribing Information, listed the following recommendations to help achieve clarity:

- type size should be such that a lower case letter 'x' was no less than 1mm in height
- lines should be no more than 100 characters in length, including spaces
- sufficient space should be allowed between lines to facilitate easy reading
- a clear style of type should be used
- there should be adequate contrast between the colour of the text and the background
- dark print on a light background was preferable
- emboldening headings and starting each section on a new line aided legibility

The Panel noted that the prescribing information in question met these requirements in relation to the number of characters per line, spacing, type style and emboldened headings. The Panel noted that most of the text met the sizing requirements but that where C_{max} and T_{max} were referred to in the 'Interactions' section, the 'max' subscript was not legible. However, given the context in which these appeared, the Panel considered that the reader would know what the subscript was.

The Panel noted that the prescribing information at issue consisted of grey text on a white background. This was not helpful. The Panel noted the recommendation in the supplementary information in relation to the contrast between text and background. The Panel considered that the prescribing information was on the limits of acceptability in this regard. However, on the whole, the Panel considered that, although not easy to read, the prescribing information did not fail to comply with the requirements of Clause 4.1 and ruled no breach of that clause. The Panel noted Lilly's intention to change the combination of font, colour and background in future material.

Complaint received **10 August 2011**

Case completed **7 September 2011**

CASE AUTH/2432/8/11

NAPP v GRÜNENTHAL

Promotion of Palexia

Napp complained about two claims in a Palexia SR (tapentadol prolonged release) leavepiece issued by Grünenthal. Palexia SR was indicated for the treatment of severe chronic pain in adults which could be managed only with opioid analgesics.

The detailed response from Grünenthal is given below.

The claim 'Introducing a new class in pain relief' was referenced to Kress (2010). Napp stated that tapentadol was an agonist at the μ-opioid receptor (MOR) (like other opioids) and also had inhibitory activity at the noradrenaline receptor (noradrenaline reuptake inhibition (NRI)) (like tramadol), and Napp did not consider that the receptor activity warranted the description 'a new class'. In addition, the anatomical therapeutic chemical (ATC) classification system grouped tapentadol with other opioids. Kress published a round table discussion 'Tapentadol and its two mechanisms of action; Is there a new pharmacological class of centrally-acting analgesics on the horizon?'. This group, a small number of European clinicians assembled by Grünenthal, concluded by merely questioning whether tapentadol should be considered a new class of medicine. Napp alleged that the claim was exaggerated and could not be substantiated.

The Panel noted that, although in the same ATC class, there were pharmacological differences between tapentadol and tramadol. It further noted Grünenthal's submission that as tapentadol was the only molecule with a MOR-NRI mode of action it was unlikely that a new ATC class would be created as this only usually occurred when there were at least two members of the group.

The Panel noted that the Palexia summary of product characteristics (SPC) stated that the medicine's pharmacotherapeutic group was 'Analgesics; opioids; other opioids'. The Panel thus did not accept that Palexia was a new class in pain relief and ruled that the claim was misleading in breach of the Code. Further, the Panel did not consider that the claim could be substantiated. The proposal that tapentadol was a new class of medicine was from a company-funded discussion group and had not been formally accepted by the wider medical community. In any event the Palexia SPC did not state a new drug class for the medicine. A breach of the Code was ruled.

Napp alleged that the three studies, on which the claim '…superior gastrointestinal tolerability' compared with oxycodone was based, were not powered for tolerability endpoints. Below the claim was a bar chart which compared the incidence of TEAEs (treatment-emergent adverse events) for Palexia SR and oxycodone CR in relation to constipation, nausea, vomiting, dry mouth and diarrhoea and a composite of nausea and vomiting. The differences were in favour of Palexia for constipation, nausea, vomiting and nausea and vomiting ($p<0.001$). The claim 'superior tolerability' was based on TEAEs which Napp submitted were any spontaneously reported adverse events occurring after the start of study medicine. Spontaneously reported adverse events gave less reliable results than specific measures designed to pro-actively seek out specific side effects. The severity of the TEAEs was not stated which Napp considered could significantly affect interpretation of the results and therefore a clinician's benefit/risk assessment of tapentadol compared with oxycodone. Similarly, the relationship of the TEAE to the study medicine was not reported. Napp alleged that this superlative claim misled by exaggeration, and could not be substantiated.

The Panel noted that the claim at issue and the bar chart were based on Lange *et al* (2010), a meta-analysis of pooled data from three studies. Each of the studies had actively collected adverse events. Napp was incorrect to imply that the claim was based only on spontaneously reported adverse events occurring after the start of the study medicine. The Panel noted that the three studies consistently showed that tapentadol had better gastrointestinal tolerability compared with oxycodone.

The Panel considered that given that the three source studies had actively collected adverse event data and that the data for constipation, nausea, vomiting and nausea and vomiting, was consistent across all three studies (and statistically significantly in favour of tapentadol) then the claim for superior gastrointestinal tolerability based on the pooled analysis by Lange *et al* was not misleading and could be substantiated. The Panel did not consider that the claim was exaggerated and nor was it a superlative. No breach of the Code was ruled.

Napp Pharmaceuticals Limited complained about two claims in a 6 page, gate-folded leavepiece (ref P10 0140) used by Grünenthal Ltd to promote Palexia SR (tapentadol prolonged release). Palexia SR was indicated for the treatment of severe chronic pain in adults which could be adequately

managed only with opioid analgesics. Napp marketed Oxycontin (oxycodone) which was indicated for moderate to severe cancer pain, post-operative pain or severe pain requiring a strong opioid.

1 Claim 'Introducing a new class in pain relief'

This claim appeared in a highlighted box at the top of page 1 of the leavepiece; it was referenced to Kress (2010).

COMPLAINT

Napp stated that tapentadol was an agonist at the μ-opioid receptor (MOR) (like morphine, oxycodone and other opioids) and also had noradrenaline reuptake inhibition (NRI) activity (like tramadol). These two mechanisms, responsible for the analgesia of tapentadol, were both found in tramadol and thus Napp did not consider that the receptor activity, and the similarity to tramadol, warranted the description 'a new class'. In addition, the anatomical therapeutic chemical (ATC) classification system grouped tapentadol with other opioids; the difference in coding related only to tapentadol being a different chemical substance within the same group, N02AX – other opioids.

Kress had published the results of a round table discussion entitled 'Tapentadol and its two mechanisms of action; Is there a new pharmacological class of centrally-acting analgesics on the horizon?'. Napp stated that the question mark at the end of the title clearly indicated that this was at discussion level only rather than acceptance. This group (a small number of European clinicians) was assembled by Grünenthal to debate the issues around class. The conclusion merely questioned whether tapentadol should be considered a new class of medicine, rather than firmly suggesting that it should be. However, it was unlikely that a small group of clinicians operating within an activity entirely funded by Grünenthal had sufficient independence or influence to dictate that tapentadol could be considered to be a new class. Indeed, Kress only suggested that a new class for tapentadol could be proposed. However, Napp believed that even the statement suggested by Grünenthal during inter-company dialogue, 'a proposed new class' did not represent the balance of independent (non-Grünenthal funded) evidence.

Napp alleged that the claim was exaggerated in breach of Clause 7.2 and could not be substantiated in breach of Clause 7.4.

RESPONSE

Grünenthal stated that whilst both tramadol and tapentadol had MOR agonist and NRI activity there were many differences between the two which would differentiate them into separate classes. The main difference between the medicines was that tramadol, in addition to MOR activation and NRI activity, combined a third mechanism of action ie inhibition of serotonin reuptake. *In vitro* and *in vivo* studies indicated that tapentadol had no relevant serotonin activity (Tzschentke *et al* 2007 and Schroder *et al* 2010). Serotonin, in contrast to noradrenaline, was also a transmitter in the descending excitatory pathway. As a result serotonin could have both an anti-nociceptive effect and a pro-nociceptive effect (Bannister *et al* 2009 and Suzuki *et al* 2004), thus questioning the value of this mechanism for reliable analgesic effects. This view was supported by the observation that generally selective serotonin reuptake inhibitors (SSRIs) had only small and inconsistent analgesic effects (Mico *et al* 2006).

Grünenthal submitted that another major difference between the two medicines was that tapentadol existed as a single enantiomer (non-racemic) (Tzschentke *et al*) while tramadol and its active M1 metabolite both existed as racemates (Grond and Sablotzki 2004). The NRI and serotonin reuptake inhibition activity of tramadol mainly resided in the (–) and (+)-enantiomer of the parent compound, respectively, whereas MOR activation resided in the (+)-enantiomer of O-desmethyl-tramadol (M1 metabolite), and to a lesser degree in (+)-tramadol itself. Thus, whereas tapentadol exerted its analgesic effects without the need for metabolic activation, with both mechanisms of action present in a constant ratio, tramadol was a pro-drug and required metabolism to achieve its main MOR activity.

The two medicines were also metabolised in very different ways. Tapentadol mainly via glucuronidation, without prior oxidation via CYP450, and so there was low potential for drug-drug interactions. Tramadol was metabolised mainly by N- and O-demethylation (N-demethylation mediated by CYP3A4 and CYP2B6 and O-demethylation mediated by CYP2D6) and glucuronidation or sulfation in the liver (Grond and Sablotzki).

Grünenthal noted Napp's submission that the ATC classification of tapentadol gave further evidence that it was not a new class of pain relief. Grünenthal submitted that the ATC classification was not always an appropriate way to define a new class for innovative new chemical entities such as tapentadol. Indeed, the ATC code website stated that '… the ATC system is not strictly a therapeutic classification system'. In the ATC system medicines were classified according to the main therapeutic use of the main active ingredient. Tapentadol had two modes of action, MOR and NRI, in a single molecule, based on preclinical data neither MOR nor NRI could be classed as the 'main active ingredient'. It could also not be considered a combination product. Whereas medicines which worked on the opioid receptors were classified as analgesic opioids (N02A), NRIs were classified as antidepressants (N06A). Given that tapentadol worked as an analgesic, it was not unreasonable, given the limitations of the current classification system, for it to be categorised within the opioid

N02A group. Furthermore, as tapentadol was currently the only molecule with a MOR-NRI mode of action it was unlikely that a new class would be created. As stated on the ATC website 'Subdivision on the mechanism of action will, however, often be rather broad, since a too detailed classification according to mode of action often will result in having one substance per subgroup which as far as possible is avoided'. Within the N02A class subgroups were differentiated at the fourth level based on their chemical structure rather than their pharmacological activity. New analgesic compounds with any opiodergic mechanism of action were entered into an undifferentiated N02AX class. Creation of a new class would usually only occur when there were at least two members of the group. The ATC codes for tapentadol and tramadol were N02AX06 and N02A02 respectively. The fact that tapentadol and tramadol had not been classified together in a new group further differentiated the two. However, given that Grünenthal proposed that tapentadol was a member of new class of pain relief based on its pharmacological mechanism of action, MOR-NRI, differentiation based on chemical structure, as was the case within the N02A class, had less relevance than if differentiation was by pharmacological mechanism.

Based on the above rationale Grünenthal did not consider the claim that tapentadol represented a new class of pain relief was exaggerated and as such was not in breach of Clause 7.2.

With regard to Kress, 'Tapentadol and its two mechanisms of action; Is there a new pharmacological class of centrally-acting analgesics on the horizon?' used to substantiate the claim, Grünenthal submitted that the question mark struck the tone of the paper and provided a hypothesis to debate in the editorial. Given that the conclusion stated '… it seems reasonable to propose that with the new analgesic drug tapentadol a new class of centrally-acting analgesics, designated MOR-NRI, has appeared on stage', this reference fully substantiated the claim of a new class for tapentadol.

Grünenthal submitted that the expert panel brought together to debate the issue consisted of eleven clinicians and pharmacologists from across Europe and the US of international acclaim. Grünenthal stated that in its view eleven experts was a sufficient number to provide a fair and balanced opinion. Given their high standing the panel members would not advocate a position for tapentadol that might question their academic credibility or integrity. As such their view on a new class for tapentadol could be considered independent and authoritative.

Grünenthal submitted that Kress adequately substantiated the claim of a new class in pain relief for tapentadol, and therefore was not in breach of Clause 7.4.

PANEL RULING

The Panel noted that, although in the same ATC class, there were pharmacological differences between tapentadol and tramadol. However, the Panel further noted Grünenthal's submission that as tapentadol was the only molecule with a MORI-NRI mode of action it was unlikely that a new ATC class would be created. The company had further submitted that creation of a new ATC class would only usually occur when there were at least two members of the group.

The Panel noted that the Palexia SPC stated that the medicine's pharmacotherapeutic group was 'Analgesics; opioids; other opioids'. In that regard the Panel did not accept that Palexia was a new class in pain relief as stated in the claim at issue. The Panel thus considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled. Further, the Panel did not consider that the claim could be substantiated. Kress, upon which Grünenthal relied for substantiation, was the output of a round table conference convened by the company to discuss *inter alia* the pharmacological profile of tapentadol. The author stated that it seemed reasonable to *propose* that tapentadol was a new class of medicine, designated MOR-NRI. This was, however, only a proposal from a company-funded discussion group and had not been formally accepted by the wider medical community. In any event the Palexia SPC did not state a new drug class for the medicine. The Panel considered that the claim could not be substantiated as alleged. A breach of Clause 7.4 was ruled.

2 Claim '…superior gastrointestinal tolerability' compared with oxycodone

The middle section of the inside spread of the leavepiece was headed 'Palexia SR – Unlock the potential of potent analgesia and fewer side effects compared to oxycodone CR'. This was followed by a subheading 'Palexia SR: Comparable pain relief to oxycodone CR', a graph and then the claim at issue '… with superior gastrointestinal tolerability'. The claim was referenced to Lange *et al* (2010) which was a pooled analysis of data from three phase 3 studies. Below the claim was a bar chart which compared the incidence of TEAEs (treatment-emergent adverse events) for Palexia SR and oxycodone CR in relation to constipation, nausea, vomiting, dry mouth and diarrhoea and a composite of nausea and vomiting. The differences were in favour of Palexia for constipation, nausea, vomiting and nausea and vomiting ($p<0.001$). The bar chart was adapted from Lange *et al*.

COMPLAINT

Napp alleged that the three pivotal source studies on which the claim was based were not powered to look at tolerability endpoints; the only gastrointestinal (GI) tolerability-specific measure in the studies was the secondary endpoint of the

patient assessment of constipation symptoms (PAC-SYM) questionnaire, one of multiple secondary endpoints used in all three studies but not referred to in the leavepiece. The claim 'superior tolerability' was based on TEAEs which Napp submitted were any spontaneously reported adverse events occurring after the start of study medicine. Napp objected to the conclusion of superior tolerability drawn from adverse event reporting for several reasons. Firstly, spontaneously reported adverse events gave less reliable, and therefore less valid, results than specific measures designed to pro-actively seek out specific side effects. To substantiate a superlative claim required data from the accurate and proactive measuring of validated GI symptom-specific measures as primary endpoints (or secondary endpoints provided that the primary endpoint was met). The severity of the TEAEs was not stated in the leavepiece and this could significantly affect interpretation of the results and therefore a clinician's benefit/risk assessment of tapentadol compared with oxycodone. For example, both groups might experience nausea, but if, on average, this was mild in one group and severe in the other, this could significantly affect the clinician's decision making. Similarly, the relationship of the TEAE to the study medicine was not reported (or even raised to aid the accurate interpretation of the leavepiece). Although Grünenthal provided an assessment of relatedness in inter-company dialogue, Napp was concerned that a superlative claim was based on unpowered adverse event data.

Napp alleged that this superlative claim misled by exaggeration, was not substantiated by the data presented alongside the claim and remained unsubstantiated in breach of Clauses 7.2, 7.4 and 7.10.

RESPONSE

Grünenthal agreed that the three primary studies (Buynak *et al* 2010, Afilalo *et al* 2010 and data on file (from study NCT00486811)) were specifically powered to detect the primary efficacy endpoint, and not GI tolerability. However, GI safety and tolerability endpoints (constipation and nausea or vomiting adverse events and PAC-SYM) were pre-specified in all three studies. Furthermore, changes from baseline of the PAC-SYM subscales and overall scores were designated as secondary endpoints. The pre-specified analysis plan for the three studies stated 'the effect of tapentadol PR compared to oxycodone CR for adverse events of nausea, vomiting and constipation during the double-blind period will be investigated. The nausea and vomiting composite event rates will be tested as well as the individual constipation event rate'. Analysis of adverse events was a requirement in registration studies and as such was seldom stated as a specific end point.

Grünenthal submitted that in all studies tapentadol PR demonstrated significant improvements in GI tolerability (constipation and nausea and/or vomiting adverse events and PAC-SYM) compared with oxycodone CR. The studies showed significant differences in GI TEAEs between active groups; tapentadol PR patients were significantly less likely to experience constipation and nausea and/or vomiting than patients in the oxycodone CR group ($p<0.001$ for all studies). An additional post-hoc analysis, showed that overall GI tolerability was also significantly different favouring tapentadol PR over oxycodone CR. Grünenthal stated that this was new data.

For PAC-SYM, the mean changes from baseline at endpoint in the overall PAC-SYM score were statistically significantly lower in the tapentadol PR groups compared with the oxycodone CR groups in all three studies ($p \leq 0.02$) indicating more severe scores in the oxycodone CR group. The differences in the mean change from baseline in abdominal, rectal and stool subscales were also statistically significantly different (with the exception of the abdominal subscale in Buynak *et al*) in favour of tapentadol PR in the three studies. These findings were consistent with the lower percentage of subjects with TEAEs of constipation observed in the tapentadol PR groups compared with the oxycodone CR groups.

Whilst tolerability was not the primary endpoint across all three studies, Grünenthal submitted that it had consistently shown statistically and clinically meaningful differences demonstrating that tapentadol PR had an improved GI tolerability compared with oxycodone CR. Given the replication of these findings in three separate independent studies, the chance that this was due to an error (ie claiming a difference based on the three trials although there was none in reality) was unlikely. In fact, similar results with improved GI tolerability for tapentadol PR compared with oxycodone CR was seen in all studies, including a one year safety study (Wild *et al* 2010). As the comparisons in all three independent studies gave significant results, Grünenthal submitted that it was not relevant that the single trials were not powered for an adverse event comparison and no formal hypothesis testing was required to accept the difference between tapentadol PR and oxycodone CR. These studies therefore provided sufficient evidence to substantiate a claim of superior GI tolerability.

Moreover, unlike the three primary studies which were not specifically powered to detect differences in GI adverse events between the two active comparators, Grünenthal submitted that the pre-planned pooled-analysis allowed for a direct comparison between oxycodone CR and tapentadol PR. The pooled analysis was calculated as having more than 99% power to show GI superiority (based on previous trial data). Demonstration of superior GI tolerability was among the primary objectives of the pooled-analysis. The pre-specified pooling of these studies demonstrated a highly significant difference ($p<0.001$) in GI TEAEs between tapentadol PR and oxycodone CR favouring tapentadol PR as a primary endpoint (Lange *et al*).

Grünenthal submitted that Lange *et al* substantiated the claim of superior GI tolerability.

Further evidence to support the claim came from the lower discontinuation rates due to adverse events seen in the tapentadol PR group (18.3%) compared with the oxycodone CR group (39.4%) in the pooled analysis in Lange *et al*. Specific rates of discontinuation due to GI adverse events, were also lower in the tapentadol PR group (8.1%), compared with oxycodone CR (24.7%) (data on file). In addition oxycodone CR patients discontinued treatment significantly earlier than tapentadol PR patients (median time to discontinuation 39 days vs 118 days respectively p<0.001).

Grünenthal submitted that, based on the evidence presented above, there was no breach of Clause 7.2.

With respect to the use of TEAEs to support the claim of superior tolerability, Grünenthal considered that these reported adverse events gave reliable and valid results about specific side effects. Collecting unsolicited adverse event reports was standard in drug safety and the accepted industry standard for adverse drug reaction determination. The collection of reported adverse events could not be validated but this did not mean the results were unreliable. Within all studies, physicians continuously and proactively monitored adverse events by using non-leading questions at each study visit (weekly during titration; eight times throughout the 12 week maintenance period), and in follow-up telephone calls. These adverse events should not be considered spontaneously reported. Adverse events were also collected through spontaneous reports from patients. All trials were double-blind and randomised which helped to avoid biased adverse event reporting between the two active treatments. This was evidenced by the consistency of the adverse events results across the three independent trials. The trials also included large numbers of patients (pooled analysis: placebo n=993; tapentadol PR n=981; oxycodone CR n=1,001, Lange *et al*) which also limited any effect of biased reporting.

Grünenthal believed that a specific validated measure of GI symptoms was not necessarily required to demonstrate differences in GI tolerability. While GI adverse events might be less sensitive at detecting differences between adverse events between active groups, in studies (such as those detailed above) where clear differences in GI tolerability were observed between active groups, Grünenthal considered GI adverse events to be adequate evidence to substantiate a superlative claim of superior GI tolerability.

Regarding the severity of the TEAEs not being defined in the leavepiece and the concern that this could significantly affect interpretation of the results and therefore the clinician's benefit/risk assessment of tapentadol PR compared with oxycodone CR, Grünenthal submitted that whilst not reported by Lange *et al*, in all of Grünenthal's clinical trials the intensity of the adverse events was scored as follows: mild – signs and symptoms which could be easily tolerated, symptoms could be ignored and disappeared when the subject was distracted; moderate – symptoms which caused discomfort but were tolerable, they could not be ignored and affected concentration; severe – symptoms affected usual daily activity. A statistical analysis on the intensity of reported GI adverse events in the pooled analysis of the three trials, showed that the oxycodone CR group reported more severe GI adverse events than the tapentadol PR group (p=0.03). Grünenthal provided a copy of top level data it had provided to Napp to substantiate this during inter-company dialogue. Napp did not ask for further details. Given that the severity of the adverse events was less in the tapentadol PR group, the bar chart in the leavepiece showing just the proportions of the GI adverse events under the title '… with superior gastrointestinal tolerability [compared to oxycodone CR]' referenced to Lange *et al* did not affect the interpretation of the results or the clinician's benefit/risk assessment of tapentadol PR compared with oxycodone CR.

Grünenthal thus submitted that the claim of superior tolerability compared with oxycodone CR was accurate, balanced and represented a fair evaluation of all the evidence, and that the claim and the bar chart below it were not misleading or in breach of Clauses 7.2, 7.4 or 7.10.

Regarding Napp's view that the relationship of the TEAE to the study medicine was not reported, therefore adverse events unrelated to the study medicine could significantly bias the quoted TEAEs and mislead the clinicians about the profile of tapentadol compared with oxycodone, Grünenthal submitted that while the relationship between the study medicine and the TEAEs was not reported, overall the majority of GI adverse events were possibly, probably or certainly related to the study medicine. The proportions were similar between the two medicines (tapentadol PR, 89%; oxycodone, CR 91%) and for both medicines 98% of constipation was considered related to the study medicine. Analysis of GI TEAEs specifically associated with the study medicine showed that the tapentadol PR group had significantly less overall GI TEAEs, nausea, vomiting and constipation than oxycodone CR (data on file). Grünenthal had provided data to Napp to substantiate this and Napp did not ask for further details. Further details and statistical analysis of the data provided to Napp was provided. Given that the majority of adverse events were related to the two active study medicines and these results were consistent for both tapentadol PR and oxycodone CR, there was no reason to believe that this would significantly bias the interpretation of the quoted figures of TEAEs reported in the publications. Therefore, by presenting a bar chart showing just the proportions of the GI adverse events under the title '… with superior gastrointestinal tolerability (compared to oxycodone CR)' referenced to Lange *et al* Grünenthal had not misled clinicians about the

profile of tapentadol PR compared with oxycodone CR. Therefore Grünenthal submitted that the claim of superior tolerability compared with oxycodone CR was accurate, balanced and represented a fair evaluation of all the evidence, and that the claim and the bar chart below it were not misleading or in breach of Clauses 7.2, 7.4 or 7.10.

PANEL RULING

The Panel noted that the claim at issue and the bar chart were based on Lange *et al* which was a meta-analysis of pooled data from three studies (data on file (from study NCT00486811), Afilalo *et al* and Buynak *et al*). A total of 2,974 patients (placebo, n=993; tapentadol, n=980 and oxycodone, n=1,001) were evaluable for safety. Each of the three studies had actively collected adverse event data. In study NCT00486811 adverse events were continually monitored or asked about using a non-leading question at each visit and follow up telephone call. Adverse events reported spontaneously by patients were also documented. Afilalo *et al* monitored adverse events throughout the study and for 10-14 days after discontinuation of the study medicine and Buynak *et al* assessed safety throughout the study using, *inter alia*, adverse event reporting. All three studies also used the PAC-SYM questionnaire. In that regard the Panel considered that Napp was incorrect to imply that the claim was based only on spontaneously reported adverse events occurring after the start of the study medicine.

The Panel noted that the three studies consistently showed that tapentadol had better GI tolerability compared with oxycodone. The percentage incidence of the various side effects was also similar across the studies eg the percentage incidence of nausea for tapentadol was 20.38% (study NCT00486811), 21.5% (Afilalo *et al*) and 20.1% (Buynak *et al*); the pooled analysis (Lange *et al*) reported a figure of 20.7%. The corresponding figures for oxycodone were 37.16%, 36.5%, 34.5% and 36.2%.

The Panel considered that given that the three source studies had actively collected adverse event data and that the data for constipation, nausea, vomiting and nausea and vomiting, was consistent across all three studies (and statistically significantly in favour of tapentadol) then the claim for superior gastrointestinal tolerability based on the pooled analysis by Lange *et al* was not misleading. The pooled data showed no statistically significant difference between the two medicines with regard to incidence of dry mouth and diarrhoea. The Panel also noted that data had been provided which demonstrated that for individual GI TEAEs there was no statistically significant difference in the distribution of the severity of such events between tapentadol and oxycodone and that treatment discontinuations due to GI TEAEs occurred more often in the oxycodone group than in the tapentadol group. No breach of Clause 7.2 was ruled. The Panel considered that the claim could be substantiated and so it ruled no breach of Clause 7.4. The Panel did not consider that the claim was exaggerated and nor was it a superlative. No breach of Clause 7.10 was ruled.

Complaint received **16 August 2011**

Case completed **26 October 2011**

CASE AUTH/2433/8/11

ANONYMOUS v JANSSEN

Promotion of Prezista

An anonymous, non-contactable prescriber alleged a Prezista (darunavir) advertisement placed by Janssen in a 'First Announcement' booklet for the British HIV Association (BHIVA) Autumn 2011 conference was misleading and did not include prescribing information. The complainant was concerned that the claim 'Simple once daily dosing in both naïve patients and those switching for tolerability and convenience' had an asterix to a small print footnote which described the individuals that this applied to. Furthermore, it was misleading that there was no reference to the fact that for all other patients Prezista was a twice daily regimen. The advertisement did not make the twice daily regimen clear. The complainant noted that none of the claims were substantiated since there was no list of references.

The detailed response from Janssen is given below.

The Panel noted that the advertisement did not contain prescribing information. Janssen's explanation that this was due to a series of process failures and the absence of several head office and agency staff involved was inadequate. In the Panel's view, the company's procedures should have been sufficiently robust such that even in the absence of key staff, compliance standards were maintained. A breach of the Code was ruled.

With regard to the claim 'Simple once daily dosing in both naïve patients and those switching for tolerability and convenience', the Panel noted from the Prezista summary of product characteristics (SPC) that a once-daily dose was only indicated for antiretroviral treatment (ART)-naïve patients or a certain population of ART-experienced patients. Other ART-experienced patients would need a twice daily dose. The Panel noted that the relevant population of ART-experienced patients was described in the footnote. However, the Code required claims in promotional material to be capable of standing alone as regards accuracy etc. In general, claims should not be qualified by the use of footnotes and the like. The Panel considered that the claim was misleading about the patient population for whom the once daily dosing was indicated; it was not clear that for some patients twice daily dosing was necessary. A breach of the Code was ruled.

The Panel did not accept that the failure to include references in itself meant that none of the claims were substantiated as alleged and ruled no breach of the Code in that regard.

An anonymous, non-contactable prescriber complained about a Prezista (darunavir) advertisement (ref UK/HIV/2011/0056) placed by Janssen in a 'First Announcement' booklet for the British HIV Association (BHIVA) Autumn 2011 conference.

COMPLAINT

The complainant stated that the Prezista advertisements came to his attention because he was interested in the content of the claims but could not find any reference which could substantiate them. The complainant also alleged that the advertisement was a little misleading and he could not find any Prezista prescribing information throughout the 20 page flyer, which was a serious omission.

The complainant was concerned that the claim 'Simple once daily dosing in both naïve patients and those switching for tolerability and convenience' had an asterix which pointed to a footnote, in very small print, which described the very individuals that this applied to. Furthermore, there was no reference to the fact that the Prezista licence stated that for all other patients, it was a twice daily regimen which the complainant considered was very important to point out to a prescriber. The complainant referred to the dosing instructions in the summary of product characteristics (SPC). The complainant considered that this was misleading, since the advertisement did not make the twice daily regimen clear. Furthermore, as the prescribing information was missing, the complainant could not check if this was the case or not; he had to check with the electronic Medicines Compendium website to check this claim.

The complainant noted that none of the claims in the advertisement were substantiated since there was no list of references.

When writing to Janssen, the Authority asked it to respond in relation to Clauses 4.1, 7.2 and 7.4.

RESPONSE

Janssen acknowledged the serious omission of the references and prescribing information. The omission was unintentional, as a result of an administrative error which led to an incomplete version of the advertisement being included in the BHIVA First Announcement.

Unfortunately, due to the absence of several of the usual head office and agency staff involved, the

advertisement was submitted for publication without going through the copy approval process which would have picked up the obvious defects in the material. Janssen accepted that a breach of Clause 4.1 had occurred. The company had identified the series of process failures that led to this unfortunate omission, and had instituted additional training for the staff involved. Janssen described steps it had take to prevent the error happening again and noted that it intended to print an acknowledgment of its error in the final BHIVA Autumn Conference Programme which would be available to conference attendees on 17 November 2011, as well as a placement of a corrected version. This would ensure that the majority of those who saw the previous advertisement would also see the corrected version.

Janssen did not agree that the claim 'Simple once daily dosing in both naïve patients and those switching for tolerability and convenience*' was misleading. The Prezista SPC recommended once daily dosing in naïve patients as well as in treatment experienced patients with no darunavir (DRV) resistant associated mutations (RAMs), HIV-1 RNA <100,000 copies/ml and CD4+ counts ≥100 cells $x10^6$/l.

The footnote to the claim was of appropriate font size, with characters being at least 1mm in height, and Janssen thus considered it was 'clear and legible'. In Janssen's view the footnote added clarity and precision to the claim, rather than altering its meaning. Had the prescribing information not been omitted, this information and references would have been available to the reader.

Janssen submitted that it could demonstrate that in treatment experienced patients, DRV-RAMs, CD4 counts <100 cells $x10^6$/l and viral loads (VL) >100,000 copies/ml were uncommon, and therefore, patients requiring twice daily dosing represented a small population subgroup, and that the claim applied to the vast majority of patients. Available data from routine clinical practice/clinical studies suggested that most patients did not harbour DRV-RAMs:

- A retrospective analysis from 1998 to 2006 showed that 83.4% of 207,910 isolates sent from routine clinical resistance testing did not harbour DRV-RAMs (Rinehart *et al* 2007).

- A more recent analysis carried out in 2009, showed that most routine clinical HIV isolates (93.9%) harboured no DRV-RAMs (De La Rosa *et al* 2010)

- In the TITAN trial 83% of 595 treatment-experienced patients harboured no DRV RAMs at baseline (DeMeyer *et al* 2007).

- The authors of the ODIN (Once-daily Darunavir In treatment-experieNced patients) study concluded: 'Therefore data from the ODIN study may be applicable to a large group of treatment experienced patients currently under treatment' (Cahn *et al* 2011)

Gupta *et al* (2008), a systematic review of patients failing first line therapies currently prescribed in clinical practice, found:

- Virological failure (VF) at 48 weeks occurred in 4.9% of non nucleoside reverse transcriptase inhibitor (NNRTI) recipients compared with 5.3% of boosted protease inhibitor (bPI)

- Of those VF patients, 53% developed resistance to NNRTIs and 0.9% developed resistance to bPI

The 2007/2008 UK Drug Resistance Database Annual Report showed that the incidence of PI resistance in HIV population was 16%. This supported the low occurrence of bPI RAMS, and indeed, even more so of DRV-RAMS.

With regard to CD4 counts/viral loads, recent (2010) data from Stethos, an international marketing and market research company that conducted an annual HIV market report based on physician-reported patient cases, found that:

- Regarding CD4 count: of 711 patients' records, of which 565 were treatment experienced, 10% had CD4+ counts less than 200 cells/mm^3

- Regarding the VL, of 705 patient records, of which 559 were treatment experienced, only 5% had VL > 100,000 copies x 10^6/l

2010 SOPHID (Survey Of Prevalent HIV Infections Diagnosed) data from the Health Protection Agency showed only 1,068 out of 56,071 HIV patients receiving care had CD4 counts 0-100.

In summary, Janssen did not believe that the claim as it appeared on the advertisement breached Clauses 7.2 and 7.4. However, as the complainant had considered otherwise and the company wished to avoid any potential ambiguity in its materials, it committed to not use this claim with the explanatory footnote in the same way in future promotional items.

PANEL RULING

The Panel noted that the single page advertisement at issue contained a number of claims for Prezista, but did not contain prescribing information. The Panel considered that Janssen's explanation that this was due to a series of process failures and the absence of several of the usual head office and external agency staff involved, was inadequate. In the Panel's view, the company's procedures should have been sufficiently robust such that even in the absence of key staff, compliance standards were maintained. The Panel was very concerned that the advertisement had not been through the Janssen copy approval process and was published without being certified. It noted Janssen's submission that it had instituted additional training for staff involved.

Nonetheless, the omission of the prescribing information was contrary to the requirements of Clause 4.1, and a breach of that clause was ruled.

With regard to the complainant's second allegation concerning the claim 'Simple once daily dosing in both naïve patients and those switching for tolerability and convenience', the Panel noted that Section 4.2 of the Prezista SPC, Posology and method of administration, stated:

- 'For ART-experienced adults with no darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥100 cells x 10^6/l, a dose regimen of 800 mg once daily with ritonavir 100 mg once daily taken with food may be used.

- In all other ART-experienced adults or if HIV-1 genotype testing is not available, the recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food. PREZISTA 75 mg and 150 mg tablets can be used to construct the twice daily 600 mg regimen. The use of 75 mg or 150 mg tablets to achieve the recommended dose is appropriate when there is a possibility of hypersensitivity to specific colouring agents, or difficulty in swallowing the 300 mg or 600 mg tablets.'

For ART-naïve patients, the recommended dose regimen was 800mg once daily with ritonavir 100mg once daily taken with food.

The Panel noted that a once-daily dose was only indicated for ART-naïve patients or a certain population of ART-experienced patients. Other ART-experienced patients would need a twice daily dose. The Panel noted Janssen's submission that the relevant population of ART-experienced patients was described in the footnote at the bottom of the page. However, the supplementary information to Clause 7 required that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like. For ART-experienced patients to receive once daily dosing of Prezista, they must have no DRV-RAMs, and a viral load and CD4 count within certain parameters. The Panel noted Janssen's submission that patients requiring twice daily dosing represented a small subgroup and the claim at issue applied to the vast majority of patients. The Panel considered that the claim at issue 'Simple once daily dosing in both naïve patients and those switching for tolerability and convenience*' was misleading about the patient population for whom the once daily dosing was indicated and did not make it clear that for some patients twice daily dosing was necessary. A breach of Clause 7.2 was ruled.

The Panel noted that the Code required references to be given in certain circumstances, such as when referring to published studies (Clause 7.6) or when using artwork etc from published studies (Clause 7.8). The Code required that material be capable of substantiation and that substantiation be provided on request (Clauses 7.4 and 7.5). The Panel did not accept that the failure to include references in itself meant that none of the claims were substantiated as alleged and ruled no breach of Clause 7.4 in that regard.

Complaint received **22 August 2011**

Case completed **4 October 2011**

CASE AUTH/2437/9/11

DOCTOR v BOEHRINGER INGELHEIM

Pradaxa email

A medical director of a primary care service provider complained that a promotional email about Pradaxa (dabigatran) had been sent by a third party to his NHS account. Pradaxa was Boehringer Ingelheim's product for prevention of stroke and systemic embolism in certain patients.

The complainant alleged that the email had been sent unsolicited. The complainant did not request any such information and had not given his email address to any party in connection with either Pradaxa or any other medicine. The complainant could not find a link to unsubscribe from the distribution list. The complainant stated that his complaint was about a breach of both UK law and the Code.

The Authority advised that it could only consider complaints within the context of the Code.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted Boehringer Ingelheim's submission that the database provider obtained consent from the complainant when he completed his registration. An email to the complainant in February 2011 described the registration process for another service and explained that from time to time information would be sent '... by e-mail about our associated/affiliated companies and their clients' product and services, which may include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information'. This was followed by a new paragraph 'However, please be advised that we will not share your e-mails with any third parties'. The unsubscribe facility which stated 'If you do not wish to receive such information please click the box*' appeared at the very end of the email after the signature and contact details. Additionally, members of the database had been emailed an opt-in policy which included the following: 'All our e-mail communications to healthcare personnel, in accordance within the Data Protection Act 2001 include an 'unsubscribe' option which allows recipients to 'opt-out' if they wish. They can 'opt-out' of receiving promotional material only and still receive official information. If a recipient chooses to 'opt-out' of receiving promotional material we will stop sending messages to that person'. The policy also referred to contact by email and telephone to update and validate information wherein recipients would be told they had opted-in to receive emails from the service provider and their affiliates which might contain promotional information. The Panel did not have a copy of the covering email providing a copy of the policy to the complainant.

The Panel noted that the database was used to email campaigns on behalf of government departments and agencies which many NHS employees would consider important information and want to receive. The Panel considered that it was not at all clear on the registration email sent to the complainant in February 2011 that he could consent to receive official information by email but choose not to receive promotional material. It was not acceptable to rely on the opt-in policy which was sent separately in this regard. Although it was clear on the registration email that the complainant would receive, *inter alia*, promotional material for medicines on registration, recipients might choose not to unsubscribe given the impression from the wording of the email and the positioning of the unsubscribe option that they would otherwise not receive any material by email including official information. This was not satisfactory and in the Panel's view should be improved. The Panel queried whether the recipient was given a *bona fide* choice. Nonetheless the Panel considered that by registering on the site and failing to unsubscribe, the complainant had given prior permission to receive, *inter alia*, promotional material by email and no breach of the Code was ruled.

The Panel noted Boehringer Ingelheim's submission that the unsubscribe facility was omitted in error from the Pradaxa email. The Panel noted that the unsubscribe option did not appear in the version of the email certified by the company. This was a serious error. A breach of the Code was ruled as acknowledged by Boehringer Ingelheim.

A medical director of a primary care service provider, complained about a promotional email (ref DBG 2624) he had received about Pradaxa (dabigatran). Pradaxa was Boehringer Ingelheim Limited's product for prevention of stroke and systemic embolism in certain patients.

COMPLAINT

The complainant alleged that the email had been sent unsolicited to his NHS email account. Pradaxa was marketed for stroke prevention in patients with atrial fibrillation (SPAF). The email referred to the SPAF academy and had a Boehringer Ingelheim

logo at the bottom along with references and prescribing information.

The complainant stated that he did not request any such information either from Boehringer Ingelheim or via any third party or pharmaceutical representative. He had not given his email address to any party in connection with either this or any other pharmaceutical product.

The complainant checked the email carefully to find out how to unsubscribe himself from the list being used to send the message and could not find any such link.

The complainant had a number of concerns:

- The Privacy and Electronic Communications (EC Directive) Regulations 2003, which applied to all organisations that sent out marketing by telephone, facsimile, email or any other form of electronic communications, provided that organisations could not send unsolicited marketing emails to individual subscribers unless the recipient had given his prior consent. The complainant noted that this would have required some form of positive action by him and he had not knowingly completed any opt-in or any opt-out form of consent.
- In line with the regulations mentioned above, Clause 9.9 stated that telephone, text messages, email, telemessages, facsimile, automated calling systems and other electronic data communications must not be used for promotional purposes, except with the prior permission of the recipient.
- Even allowing for the above, the sender had made no provision for the recipient to request that they be unsubscribed from the mailing list or to prevent any further unsolicited email (spam).
- The sender had not made it clear how the recipient came to be on the mailing list or for what purpose their details were originally collected.

The complainant stated that his complaint was about a breach of both UK law and the Code.

When writing to Boehringer Ingelheim, the Authority advised that it could only consider complaints within the context of the Code; it could not consider matters under UK law. The company was asked to respond in relation to Clause 9.9 as cited by the complainant.

RESPONSE

Boehringer Ingelheim firmly asserted that the email received by the complainant from the third party database provider was in part compliant with Clause 9.9 after the complainant's consent by opting-in and registering for the same. A copy of the agreement was provided. The database provider had agreed with Boehringer Ingelheim to include a prominent opt-out link at the end of the email as was its usual practice.

Boehringer Ingelheim had a contract with the database provider as a third party through another organisation for the Pradaxa email campaigns.

Boehringer Ingelheim explained that the database was part of a permission-based secure database which supplied details of doctors to members signed up to receive this type of information. It had evolved into providing permission based secure online messaging collating email addresses of doctors registered within the UK. Similar to other media partners, it was a private company that had developed this facility which was used by the NHS but also by third parties to complete secure online messaging where permission had been granted.

The database provider had sent email campaigns on behalf of many government departments and agencies. Details were given.

In line with usual process, consent was obtained from the complainant when he completed his registration. Consent highlighted the following, '… will from time to time send information by e-mail about our associated/affiliated companies and their clients' product and services, which may include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information'. It also gave an option to opt-out of this registration as, 'If you do not wish to receive such information please click the box*'.

This was also highlighted in the 'opt-in' policy, which all signed up members of the database would have received via their registered email address.

Unfortunately in the email at issue the opt-out option was left out in error by the database provider, for which it had taken full responsibility. Boehringer Ingelheim noted that the opt-out option to these kinds of email was still in place on the main registration form.

The database provider had assured Boehringer Ingelheim and taken steps to make sure this did not happen again. As a corrective measure the unsubscribing option would be made available to the recipients of the original email.

In summary, the email received by the complainant was with his consent and the database provider had agreed with Boehringer Ingelheim to include a prominent opt-out link at the end of the email as was its usual practise. However, given the absence of the opt-out function in this instance, Boehringer Ingelheim admitted a breach of Clause 9.9.

PANEL RULING

The Panel noted that the complainant had received via his NHS email account a promotional email for Pradaxa. The Panel noted that Clause 9.9 prohibited the use of email for promotional purposes except with the prior permission of the recipient. The Panel

noted that Boehringer Ingelheim via a third party had a contract with the database provider for Pradaxa email campaigns.

The Panel noted Boehringer Ingelheim's submission that the database provider obtained consent from the complainant when he completed his registration. An email to the complainant in February 2011 described the registration process for another service and explained that it '… will from time to time send information by e-mail about our associated/affiliated companies and their clients' product and services, which may include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information'. This was followed by a new paragraph 'However, please be advised that we will not share your e-mails with any third parties'. The unsubscribe facility which stated 'If you do not wish to receive such information please click the box*' appeared at the very end of the email after the signature and contact details. In addition the Panel noted that all members of the database had been emailed an opt-in policy for the service provider which included the following statement 'All our e-mail communications to healthcare personnel, in accordance within the Data Protection Act 2001 include an 'unsubscribe' option which allows recipients to 'opt-out' if they wish. They can 'opt-out' of receiving promotional material only and still receive official information. If a recipient chooses to 'opt-out' of receiving promotional material we will stop sending messages to that person'. The policy also referred to contact by email and telephone to update and validate information wherein recipients would be told they had opted-in to receive emails from the service provider and their affiliates which might contain promotional information. The Panel did not have a copy of the covering email providing a copy of the policy to the complainant.

The Panel noted that the database provider sent email campaigns on behalf of government departments and agencies which many NHS employees would consider important information and want to receive. The Panel considered that it was not at all clear on the registration email sent to the complainant in February 2011 that he could consent to receive official information by email but choose not to receive promotional material. It was not acceptable to rely on the opt-in policy which was sent separately in this regard. Although it was clear on the registration email that the complainant would receive, *inter alia*, promotional material for medicines on registration, recipients might choose not to unsubscribe given the impression from the wording of the email and the positioning of the unsubscribe option that they would otherwise not receive any material by email including official information. This was not satisfactory and in the Panel's view should be improved. The Panel queried whether the recipient was given a *bona fide* choice. Nonetheless the Panel considered that by registering on the site and failing to unsubscribe the complainant had given prior permission to receive *inter alia* promotional material by email. No breach of Clause 9.9 was ruled.

The Panel noted that the supplementary information to Clause 9.9 required that where prior permission to use emails for promotional purposes had been granted each email should have an unsubscribe facility. The Panel noted Boehringer Ingelheim's submission that the unsubscribe facility was omitted in error from the Pradaxa email by the database provider. The Panel noted that the unsubscribe option did not appear in the version of the email certified by the company. This was a serious error. The Pradaxa email did not feature an unsubscribe link and in this regard, as acknowledged by Boehringer Ingelheim, was in breach of Clause 9.9 of the Code. A breach of that clause was ruled accordingly.

Complaint received	**21 September 2011**
Case completed	**31 October 2011**

CODE OF PRACTICE REVIEW – November 2011

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

2403/5/11	**General Practitioner v Boehringer Ingelheim**	**Press article about Pradaxa**	**Breach Clause 22.2**	**No appeal**	**Page 3**
2404/5/11	**General Practitioner v Boehringer Ingelheim**	**Promotion of Pradaxa**	**Breaches Clauses 2, 3.2, 9.1, 22.1 and 22.2**	**No appeal**	**Page 7**
2407/6/11	General Practitioner v Boehringer Ingelheim	Promotion of Pradaxa	No breach	No appeal	Page 13
2409/6/11	**Anonymous v Cephalon**	**Qualification of medical signatory**	**Breach Clause 14.1**	**No appeal**	**Page 17**
2412/6/11	Anonymous v Lilly	Provision of Byetta samples	No breach	No appeal	Page 21
2413/6/11	**Voluntary admission by Leo**	**Promotion of Xamiol to the public**	**Breach Clause 22.1**	**No appeal**	**Page 24**
2415/6/11	**Director v Biogen Idec**	**Tysabri DVD**	**Breaches Clauses 9.1 and 22.1**	**No appeal**	**Page 26**
2417/6/11	**Head of Medicines Management v Servier**	**Promotion of Procoralan**	**Breach Clause 3.2 Two breaches Clause 9.1**	**Report from Panel to Appeal Board Appeal by respondent**	**Page 30**
2418/7/11	**Pharmacist v Astellas Pharma**	**Promotion of Protopic**	**Breach Clause 3.2**	**Appeals by complainant and respondent**	**Page 45**
2420/7/11	Member of the public v Biogen Idec	Tysabri on-line advertisement	No breach	Appeal by respondent	Page 51
2421/7/11	Anonymous v Roche	Conduct of representative	No breach	No appeal	Page 58
2423/7/11	**Pharmacosmos v Vifor Pharma**	**Ferinject leavepiece**	**Two breaches Clause 7.2**	**No appeal**	**Page 62**
2430/8/11	**GlaxoSmithKline Consumer Healthcare v Johnson & Johnson**	**Promotion of Nicorette QuickMist**	**Two breaches Clause 7.2**	**No appeal**	**Page 65**
2431/8/11	General Practitioner v Lilly	Legibility of prescribing information	No breach	No appeal	Page 69
2432/8/11	**Napp v Grünenthal**	**Promotion of Palexia**	**Breaches Clauses 7.2 and 7.4**	**No appeal**	**Page 70**
2433/8/11	**Anonymous v Janssen**	**Promotion of Prezista**	**Breaches Clauses 4.1 and 7.2**	**No appeal**	**Page 76**
2437/9/11	**Doctor v Boehringer Ingelheim**	**Pradaxa email**	**Breach Clause 9.9**	**No appeal**	**Page 79**

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 organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the sponsorship of attendance at meetings organised by third parties
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio or video-recordings in any format, broadcast media, non-print media, the Internet, interactive data systems and the like.

It also covers:

- the provision of information on prescription only medicines to the public either directly or indirectly, including by means of internet
- relationships with patient organisations
- the use of consultants
- non-interventional studies of marketed medicines
- the provision of items for patients
- the provision of medical and educational goods and services
- grants and donations to institutions.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the four members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. One member of the Panel acts as case preparation manager for a particular case and that member is neither present nor participates when the Panel considers it.

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. Independent members, including the Chairman, are always in a majority when matters are considered by the Appeal Board.

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 under the Code should be sent to the Director of the Prescription Medicines Code of Practice Authority, 7th Floor, Southside, 105 Victoria Street, London SW1E 6QT

telephone 020 7747 8880
facsimile 020 7747 8881
by email to: complaints@pmcpa.org.uk.