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**