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**