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**