GENERAL PRACTITIONER v BOEHRINGER INGELHEIM

e-Promotion of Pradaxa

A general practitioner complained about the promotion of Pradaxa (dabigatran) by Boehringer Ingelheim on a third party website.

Pradaxa (75mg and 110mg) was indicated for primary prevention of venous thromboembolic events in adults who had undergone elective total hip or total knee replacement surgery. Pradaxa (110mg and 150mg) was indicated for the prevention of stroke and systemic embolism in certain adult patients.

The detailed response from Boehringer Ingelheim is given below.

The complainant noted that a clinical paper summary, 'Dabigatran versus warfarin in patients with atrial fibrillation', provided on the website, referred only to the relative risk in relation to the key efficacy outcomes for dabigatran 150mg/110mg vs warfarin. A breach of the Code was alleged.

The complainant further noted that the clinical summary provided hyperlinks to the reprints of the two papers by Connolly *et al* (2009 and 2010) that it was based upon. These reprints could be downloaded and printed; the complainant alleged that this promotional facility necessitated the provision of prescribing information and its omission was in breach of the Code.

The Panel noted that the supplementary information to the Code stated, inter alia, that relative risk should never be referred to without also referring to the absolute risk. Absolute risk could be referred to in isolation.

The Panel noted that a table of data in the clinical paper summary, inter alia, referred to the relative risk stroke or systemic embolism according to treatment group. The absolute rates were also stated thus the Panel ruled no breach of the Code.

The Panel noted that the page in question provided a prominent and direct link to the prescribing information. In the Panel's view this was the first part of the material. The hyperlinked publications were part of the same material and in that regard did not also need to include links to the prescribing information. The Panel considered that prescribing information had been provided as required. No breach of the Code was ruled.

The Panel considered that by providing hyperlinks to the two Connolly *et al* papers, Boehringer Ingelheim had, in effect, invited readers to access the publications. This was a solicited request not an unsolicited request as alleged and therefore no breach was ruled.

The complainant noted that on another page headlined Pradaxa for use in stroke prevention in atrial fibrillation as were the specifics of the licensed indication. The reader was not informed that this indication was restricted only to Pradaxa 150mg and 110mg and not 75mg which was also available but for a different indication. The complainant alleged that this was misleading by omission.

The complainant noted that again this page facilitated access to reprints and prescribing information had been omitted.

The Panel noted that the licensed dose for Pradaxa in the prevention of stroke and systemic embolism in patients with atrial fibrillation was 150mg twice daily reduced to 110mg twice daily in certain patients. Pradaxa 75mg was not licensed for this indication but could be used in the primary prevention of venous thrombotic events in elective total hip or knee replacement surgery. The Panel noted that the page in question did not refer to any dose of Pradaxa but, as in the above, provided a link to the prescribing information on a red band running across the top of the page. The Panel considered that reference to the 75mg dose on this page was not required, given that it related only to the use of Pradaxa in the prevention of stoke and atrial fibrillation. No breach of the Code was ruled.

The Panel noted that a subsection of the page at issue was headed 'Clinical paper summaries*' and below this were links to these summaries. The asterisk referred to a footnote which read 'Promotional information by Boehringer Ingelheim'. Clicking on the links opened up the clinical paper summaries from which the reader could click to access, inter alia, the prescribing information. The Panel noted, therefore, that the prescribing information was accessible not only from the first page but also from the hyperlinked pages. The requirement to provide prescribing information had been met and no breach of the Code was ruled.

The Panel noted its comments above with regard to the provision of solicited and unsolicited reprints and considered that they also applied here. No breach of the Code was ruled.

A general practitioner, complained about the promotion of Pradaxa (dabigatran) by Boehringer Ingelheim Limited on a third party website.

The complainant stated that he had no interest to declare other than to state that Boehringer Ingelheim's staff and activities had done little to improve the image of the UK pharmaceutical industry. However, his scrutiny of its activities had enhanced his understanding of the Code which was the only silver lining when it came to this clearly disreputable company.

Pradaxa (75mg and 110mg) was indicated for primary prevention of venous thromboembolic events in adults who had undergone elective total hip or total knee replacement surgery. Pradaxa (110mg and 150mg) was indicated for the prevention of stroke and systemic embolism in certain adult patients.

When writing to Boehringer Ingelheim, the Authority asked it to consider Clauses 4.1 and 7.2 of the Code. The Authority also noted that the provision of prescribing information with reprints was referred to in the supplementary information to Clause 10.1.

1 Reference to absolute risk and relative risk and the provision of prescribing information

COMPLAINT

The complainant referred to the provision of the clinical paper summary entitled 'Dabigatran versus warfarin in patients with atrial fibrillation' (ref DBG2430) and noted that the results presented in table 1 only reported the relative risk in relation to the key efficacy outcomes for dabigatran 150mg/110mg vs warfarin. The complainant alleged that the omission of the absolute risk values was in breach of the Code.

The complainant further noted that the clinical summary provided hyperlinks to the full paper reprints of the two papers by Connolly *et al* (2009 and 2010) that it was based upon. These reprints could be downloaded and printed; this promotional facility was organised by Boehringer Ingelheim with the aim of providing further promotional information about dabigatran. This therefore necessitated the provision of prescribing information which had been omitted in breach of the Code.

RESPONSE

Boehringer submitted that table 1 was based on the two publications, referred to in the clinical paper summary, by Connolly *et al* in which the absolute rates of stroke or systemic embolism were prominently given for the three treatment groups (dabigatran 110mg, dabigatran 150mg and warfarin) in the Randomized Evaluation of Long-Term Anti-coagulation Therapy (RE-LY) study. From table 1 it could be seen that these values were respectively 1.54%/year, 1.11%/year and 1.71%/year. The relative risk (95% confidence interval (CI)) and p values were also clearly presented in the table. The supplementary information to Clause 7.2 stipulated that relative risk should not be given without absolute risk as this could mislead the reader. In addition, table 1 was a faithful representation of the table as it appeared in the publication. Boehringer Ingelheim therefore firmly asserted that since the absolute rates were presented in table 1 alongside relative risk, there was no breach of Clause 7.2.

With regard to the hyperlink to the two papers by Connolly *et al*, Boehringer Ingelheim stated that this information was provided because it wanted the data relating to dabigatran to be readily available for prescribers to facilitate good understanding and good prescribing. The information was consistent with the summary of product characteristics (SPC) for Pradaxa and so Boehringer Ingelheim considered that the use of these papers was appropriate and complied with the Code.

Boehringer Ingelheim submitted that at the top of the page of the website there was a link to the prescribing information which was clearly prominent and positioned (reader's view) to the right hand side of the red banner. Boehringer Ingelheim therefore disagreed that prescribing information was not readily available for review by the reader. The supplementary information to Clause 10.1 stated that an unsolicited reprint of an article about a medicine should be accompanied by prescribing information. The hyperlink was found at the bottom of the page 'Connolly SJ, *et al*. Newly identified events in the RE-LY trial' N Engl J Med 2010;363:1875-1876.' Boehringer Ingelheim argued that in this instance the provision of the article was not unsolicited: on the website there was no indication nor promotion of the availability of reprints through downloading from the NEJM website; the reader must choose to click on the hyperlink without the knowledge of where or what they would be linked to; equally once on the NEJM website again the reader must choose whether or not to print the article. Given these factors Boehringer Ingelheim strongly believed that the article was not unsolicited (ie the reader had solicited it themselves) and so the provision of prescribing information for downloading was not required. Boehringer Ingelheim therefore strongly asserted that there was no breach of Clause 10.1.

The prescribing information was legible; linked and positioned prominently within the website and consistent with the SPC. Boehringer Ingelheim therefore asserted that there was no breach of Clause 4.1.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.2 stated that referring only to relative risk, especially with regard to risk reduction, could make a medicine appear more effective than it was. In order to assess the clinical impact of an outcome, the reader also needed to know the absolute risk involved. In that regard relative risk should never be referred to without also referring to the absolute risk. Absolute risk could be referred to in isolation.

The Panel noted that table 1 referred to the relative risk and p value of stroke or systemic embolism in patients treated with dabigatran 110mg vs warfarin (0.90; p=0.30) or dabigatran 150mg vs warfarin (0.65; p<0.001). The absolute rates (% patients/year) of stroke or systemic embolism in patients treated with dabigatran 110mg (1.54%/year), dabigatran 150mg (1.11%/year) or warfarin (1.71%/year) were also stated. In that regard the Panel considered that the requirements of Clause 7.2 in relation to relative and absolute risk had been satisfied. No breach of Clause 7.2 was ruled.

The Panel noted that the webpage in question promoted the use of Pradaxa for stroke prevention in atrial fibrillation. Running across the top of the page was a red band upon which the reader could click to access, inter alia, the prescribing information. The page also provided hyperlinks to the two Connolly *et al* publications. In that regard the Panel considered

that the publications themselves were part of the promotional campaign.

The Panel considered that the supplementary information to Clause 4.1, Electronic Journals, was relevant to the material before it. The supplementary information stated that the first part of an advertisement in an electronic journal, such as the banner, was often the only part of the advertisement that was seen by readers. It must therefore include a clear, prominent statement as to where the prescribing information could be found. This should be in the form of a direct link. The first part was often linked to other parts and in such circumstances the linked parts would be considered as one advertisement.

The Panel noted that the webpage in question provided a prominent and direct link to the prescribing information. In the Panel's view this was the first part of the material. The hyperlinked publications were part of the same material and in that regard did not also need to include links to the prescribing information. The Panel considered that prescribing information had been provided as required. No breach of Clause 4.1 was ruled.

The Panel noted that Clause 10.1 stated that reprints of articles in journals must not be provided unsolicited unless the articles had been refereed. The supplementary information to that clause stated that when providing an unsolicited reprint of an article about a medicine, it should be accompanied by prescribing information.

The Panel considered that by providing hyperlinks to the two Connolly *et al*, papers, Boehringer Ingelheim had, in effect, invited readers to access the publications. This was therefore a solicited request for the papers. In that regard the Panel did not consider that Clause 10.1 was relevant and so no breach of that clause was ruled.

2 Indication of licensed doses and the provision of prescribing information

COMPLAINT

The complainant referred to another page of the website (ref DBG2686) and noted that Pradaxa for use in stroke prevention in atrial fibrillation was headlined on this page as were the specifics of the licensed indication. The complainant further noted, however, that the reader was not informed that this indication was restricted only to Pradaxa 150mg and 110mg and not 75mg which was also available but for a different indication. The complainant alleged that this was misleading by omission.

The complainant noted that again this webpage facilitated access to reprints and as per point 1 above, prescribing information that should have been associated with, or accompanied, the reprints had been omitted.

RESPONSE

Boehringer Ingelheim noted that as Pradaxa 75mg was not licensed for stroke prevention in atrial fibrillation, to have provided the SPC for that medicine following a reference to stroke prevention in atrial fibrillation would have been inappropriate and confusing for the reader. Boehringer Ingelheim did not consider that it was misleading by omission not to refer to Pradaxa 75mg in this context. Boehringer Ingelheim proposed the opposite, namely that to refer to it here would be misleading. The complainant objected that the prescribing information was not available here but this was incorrect as it was available in the top right hand corner of the page, as before, in the form of a white on red hyperlink.

In summary Boehringer Ingelheim firmly asserted that there were no breaches of the Code in the materials referred to above and specifically no breaches of Clauses 4.1, 7.2 and 10.1.

Boehringer Ingelheim confirmed that it paid for the materials to be included on www.doctors.net.uk.

PANEL RULING

The Panel noted that the licensed dose for Pradaxa in the prevention of stroke and systemic embolism in patients with atrial fibrillation was 150mg twice daily reduced to 110mg twice daily in patients aged 80 years or over and patients with an increased risk of bleeding. Pradaxa 75mg was not licensed for this indication but could be used in the primary prevention of venous thrombotic events in elective total hip or knee replacement surgery. The Panel noted that the webpage in question did not refer to any dose of Pradaxa but, as in point 1 above, provided a link to the prescribing information on a red band running across the top of the page. The Panel noted that the title of the webpage was 'Pradaxa – stroke prevention in atrial fibrillation'. The Panel considered that reference to the 75mg dose on this webpage was not required, given that it related only to the use of Pradaxa in the prevention of stoke and atrial fibrillation. The Panel did not consider that the webpage was misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that a subsection of the page at issue was headed 'Clinical paper summaries*' and below this were links to these summaries. The asterisk referred to a footnote which read 'Promotional information by Boehringer Ingelheim'. Clicking on the links opened up the clinical paper summaries. Running across the top of each summary was the same red band as before upon which the reader could click to access, *inter alia*, the prescribing information. The Panel noted, therefore, that the prescribing information was accessible not only from the first page but also from the hyperlinked pages. The Panel considered that the requirement to provide prescribing information had been met. No breach of Clause 4.1 was ruled.

The Panel noted its comments above with regard to Clause 10.1 and considered that they also applied here. No breach of Clause 10.1 was ruled.

Complaint received **15 November 2011**

Case completed **2 February 2012**