PHARMACIST v BOEHRINGER INGELHEIM

Promotion of Pradaxa

A pharmacist complained about stroke prevention leavepieces for Pradaxa (dabigatran) 110mg bd and 150mg bd and the conduct of a representative presenting a Pradaxa detail aid produced by Boehringer Ingelheim.

The complainant alleged that the title of the leavepieces 'Stroke Prevention' was misleading. Pradaxa was not licensed for stroke prevention but for prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with certain risk factors. The complainant submitted that although the front pages of the leavepieces further down referred to nonvalvular atrial fibrillation, this was not clear on first inspection.

The leavepieces went on to state that dabigatran was generally as well tolerated as warfarin. The complainant stated that in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, more patients discontinued treatment due to poor tolerability. Major bleeding was no more frequent between the groups assigned to warfarin, dabigatran 110mg bd or 150mg bd, however the higher risk of gastrointestinal (GI) side effects and GI bleeding (with 150mg bd) compared with warfarin brought in to question its use in those at risk of these effects. The trial only considered data for two years therefore long term safety was unclear.

The complainant had attended a nurse education meeting at which a Boehringer Ingelheim representative presented and had glossed over the GI side effects and stated that 'PPI [proton pump inhibitor] cover might be required'. The representative also did not mention the increased rate of myocardial infarctions (MIs) with high dose dabigatran.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that the licensed indication was stated in full prominently on the front page of both leavepieces and positioned such that it would be read in conjunction with the main claim 'Stroke Prevention'. The full indication would be immediately obvious. Given its context the Panel did not consider that the claim 'Stroke Prevention' on the front page of either leavepiece was misleading or inconsistent with the Pradaxa summary of product characteristics (SPC) as alleged. No breaches of the Code were ruled including Clause 2.

The Panel noted that both leavepieces included the prominent claim that 'In RE-LY, Pradaxa was generally as well tolerated as warfarin'. Beneath the claim was a number of bullet points and additional information.

Data from the RE-LY study (Connolly *et al* 2009) showed that the discontinuation rates for both doses of Pradaxa were statistically significantly higher at 1 year and 2 years vs warfarin ($p<0.001$). Reasons for discontinuation showed, inter alia, that 2.7% of patients discontinued Pradaxa (110mg and 150mg) therapy due to serious adverse events vs 1.7% of patients assigned to warfarin ($p<0.001$). GI symptoms (including pain, diarrhoea and vomiting) prompted 2.2% of patients in the Pradaxa 110mg group to discontinue therapy, 2.1% of patients in the Pradaxa 150mg group and 0.6% in the warfarin group. These differences were not statistically significant. GI bleeding resulted in the discontinuation of therapy in 1%, 1.3% and 0.9% of patients taking Pradaxa 110mg, 150mg and warfarin, respectively. These differences were not statistically significant. Adverse events reported in any of the three treatment groups were comparable with the exception of dyspepsia which was reported by 11.8% of patients in the Pradaxa 110mg group, 11.3% of patients in the Pradaxa 150mg group and 5.8% of patients taking warfarin ($p<0.001$ for the comparison of either dose of Pradaxa and warfarin).

The Panel noted that discontinuation rates, rates of dyspepsia and bleeding reactions were discussed in bullet points beneath the claim at issue. These, however, were in a much smaller black font size whereas the claim at issue was separate and visually prominent in a larger, blue font.

The Panel considered that given the statistically significant differences between Pradaxa and warfarin with regard to dyspepsia and discontinuation of therapy because of serious adverse events, the prominent claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' did not reflect the balance of evidence and was misleading in that regard. Breaches of the Code were ruled in relation to each leavepiece. These rulings were appealed.

The leavepiece for Pradaxa 110mg included a page headed 'Rates of bleeding vs warfarin' beneath which was the prominent claim 'Significantly lower rates of any, major and life-threatening bleeding vs warfarin'. The Panel noted that one of the bullet points below the claim stated that GI bleeding was higher with Pradaxa 110mg but not significantly so. In that regard the Panel did not consider that the claim 'Significantly lower rates of any, major and life-threatening bleeding vs warfarin' reflected the evidence. The claim was misleading with regard to the incidence of GI bleeding and breaches of the Code were ruled. These rulings were appealed.

The leavepiece for Pradaxa 150mg also included a page headed 'Rates of bleeding vs warfarin'.

Beneath the heading was the prominent claim 'Similar rates of major bleeding vs warfarin (primary safety outcome)'. One of the bullet points beneath the claim stated that GI bleeding was significantly higher with Pradaxa 150mg bd (warfarin, 1.07; Pradaxa 1.57: p=0.0008). The RE-LY study stated that there was a significantly higher rate of major GI bleeding with Pradaxa 150mg than with warfarin. The Panel thus considered that with regard to major GI bleeds the claim 'Similar rates of major bleeding vs warfarin (primary safety outcome)' did not reflect the balance of the data. The claim was misleading in that regard. Breaches of the Code were ruled. These rulings were appealed.

The Panel did not consider that the leavepieces were misleading with regard to the length of time that data had been collected. No breach of the Code was ruled.

The Panel noted that the complainant had alleged that a representative at a meeting had glossed over GI side effects and stated that PPI cover might be required. It was also alleged that the representative did not mention the increased rate of MI with high dose Pradaxa.

The Panel noted that the detail aid used by the representative was about Pradaxa 150mg. With regard to the tolerability of Pradaxa vs warfarin and the incidence of GI symptoms the Panel noted that page 8 of the detail aid was the same as that discussed above for the Pradaxa 150mg leavepiece. The Panel thus considered that the claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' was misleading as above and that its rulings of breaches of the Code also applied here. These rulings were appealed.

The Panel noted that the relevant part of the representatives' briefing document stated that the bullet points below the claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' provided an overview of side-effects associated with Pradaxa 150mg bd. It was noted that the section provided practical guidance on managing dyspepsia (including reference to the permitted use of a concomitant PPI in the RE-LY study) and top line information about rates of MI.

With regard to the allegation that the representative had 'glossed over' GI side-effects the Panel noted it was difficult in such circumstances to determine precisely what had been said. The dyspepsia data appeared under a heading of 'generally as well tolerated as warfarin' but the briefing material had specifically drawn the representatives' attention to the management of dyspepsia. The SPC for Pradaxa 150mg stated that the administration of a PPI could be considered to prevent GI bleeding. Although noting its rulings above, the Panel, on balance, considered that on this narrow point the briefing material was not unreasonable. No breach of the Code was ruled.

The Panel noted its rulings on the representatives' briefing document and detail aid. There was no way of knowing exactly what the representative had said about GI side-effects and the Panel thus ruled no breach of the Code.

The Panel noted that both parties agreed that MI data had not been discussed at the meeting. The complainant had submitted that there was an increased rate of MI with high dose Pradaxa. The Panel noted, however, that the RE-LY study showed that although there was an increased annual MI rate in patients taking Pradaxa 150mg vs warfarin the difference was not statistically significant. The data from the RE-LY study regarding MI rate was included on page 8 of the detail aid and in each of the leavepieces provided to delegates. The Panel had no evidence before it to show that by not discussing the MI data the representative had given a misleading impression of the safety of Pradaxa as alleged. No breach of the Code was ruled.

The Panel noted its rulings above and considered that overall the materials at issue minimised a prescriber's concerns about the side effect profile of Pradaxa. The materials were misleading with regard to serious adverse events including major GI bleeding and also about the incidence of dyspepsia with Pradaxa. The Panel was concerned that the material had the potential to compromise patient safety. High standards had not been maintained. A breach of the Code was ruled which was appealed. With regard to Clause 2 the Panel considered that providing unbalanced and misleading information about the incidence of GI bleeding and major GI bleeds was a serious matter. The materials in question were such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed.

The Appeal Board considered that the claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' would be taken to mean that in most respects Pradaxa was as well tolerated as warfarin. In that regard readers would accept that some side-effects might occur more often with Pradaxa than warfarin (and vice versa) whereas for other side-effects there might be little difference between the medicines. The Appeal Board considered that readers would be familiar with the side-effect profile of warfarin and know that it had some problems with regard to tolerability. The Appeal Board noted the detailed information below the claim at issue, which, inter alia, referred to increased rates of discontinuation ($p<0.01$), dyspepsia ($p<0.01$) and myocardial infarction (p=ns) for Pradaxa 150mg and 110mg and considered on balance that given the context in which it appeared, the claim at issue was not misleading. The Appeal Board ruled no breaches of the Code in relation to both leavepieces. The appeals on this point were thus successful.

With regard to the Pradaxa 110mg leavepiece the Appeal Board noted that the claim 'Significantly lower rates of any, major and life-threatening bleeding vs warfarin' appeared above four bullet points. Three of the four bullet points had details of the statistically significant advantages of Pradaxa 110mg compared with warfarin for 'Any bleeding

(major or minor)', 'Major bleeding' and 'Life-threatening bleeding'. The fourth bullet point stated that 'Gastrointestinal bleeding was higher with Pradaxa 110mg … but not significantly so …'. In the Appeal Board's view, the meaning of 'any' in the claim at issue, was not clear but considered that, given the additional detailed information immediately below it, on balance, the claim was not misleading. No breaches of the Code were ruled. The appeal on this point was successful.

With regard to the 150mg leavepiece the Appeal Board noted that the claim 'Similar rates of major bleeding vs warfarin (primary safety outcome)' was followed by three bullet points which gave more detailed information. The Appeal Board noted that from the bullet points that 'Any bleeding (major or minor)' and 'Life-threatening bleeding' were statistically significantly lower with Pradaxa 150mg compared with warfarin and 'Gastrointestinal bleeding' was statistically significantly higher with Pradaxa 150mg. The Appeal Board thus considered that, given the context in which it appeared, the claim was not misleading. No breach of the Code was ruled. The appeal on this point was thus successful.

The Appeal Board noted that page 8 of the detail aid also featured the claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' and in that regard it considered that its ruling above about the use of the claim in the leavepieces applied here. No breaches of the Code were ruled. The appeal on this point was thus successful.

The Appeal Board noted its rulings above and consequently ruled no breach of the Code was ruled including Clause 2. The appeal on this point was thus successful.

A pharmacist complained about stroke prevention leavepieces for Pradaxa (dabigatran) 110mg bd and 150mg bd and the conduct of a representative presenting the information contained within the Pradaxa detail aid. Pradaxa was marketed by Boehringer Ingelheim for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation and one or more stated risk factors.

COMPLAINT

The complainant alleged that the title of the leavepieces 'Stroke Prevention' was misleading. Pradaxa was not licensed for stroke prevention but for prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

- Previous stroke, transient ischemic attack, or systemic embolism (SEE)
- 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

The complainant submitted that although the leavepieces further down referred to nonvalvular atrial fibrillation, this was not clear on first inspection. The leavepieces went on to state that dabigatran was generally as well tolerated as warfarin. The complainant stated that in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, more patients discontinued treatment due to poor tolerability. Major bleeding was no more frequent between the groups assigned to warfarin, dabigatran 110mg bd or 150mg bd, however the higher risk of gastrointestinal (GI) side effects and GI bleeding (with 150mg bd) compared with warfarin brought in to question its use in people who were at risk of these effects. The complainant submitted that the trial only considered data for two years therefore long term safety was unclear.

The complainant had attended a nurse education meeting in October, at which a Boehringer Ingelheim representative presented and had glossed over the GI side effects and stated that 'PPI [proton pump inhibitor] cover might be required'. The representative also did not mention the increased rate of myocardial infarctions (MIs) with high dose dabigatran.

When writing to Boehringer Ingelheim, the Authority asked it to consider the requirements of Clauses 3.2, 7.2, 7.9, 15.2, 15.9, 9.1 and 2 of the Code.

RESPONSE

Boehringer Ingelheim submitted that the lunchtime meeting in question was a legitimate meeting held in NHS premises organised by the GP surgery. This type of meeting gave representatives an opportunity to present product information to health professionals. The meeting was attended by five practice nurses. The representative used the certified sales aid for Pradaxa (ref DBG 2764) and attendees were also given the two leavepieces at issue and a Pradaxa educational pack (DBG 2653) (copies of all materials were provided). The marketing authorization for Pradaxa and agreement with the Medicines and Healthcare products Regulatory Agency (MHRA) required Boehringer Ingelheim to make copies of the Pradaxa educational pack available to all potential prescribers. The pack consisted of the prescriber guide (DBG 2466), summaries of product characteristics (SPCs) for Pradaxa 110mg (DBG 2687) and Pradaxa 150mg (DBG 2637) and a patient alert card (DBG 2464). The pack was also offered to other health professionals (eg nurses, pharmacists, etc). Boehringer Ingelheim noted that all of the materials used at the meeting had been pre-vetted by the MHRA. There was no formal agenda for the meeting; however, as mentioned above, there was a discussion using the Pradaxa detail aid.

Boehringer Ingelheim submitted that the title 'Stroke Prevention', which appeared on the first page of the

detail aid and leavepieces, included the full licensed indication for Pradaxa positioned directly underneath it. Boehringer Ingelheim therefore considered that the title could not be read in isolation nor could it be unclear (as the complainant alleged) since the full licensed indication could not be ignored or missed and hence it refuted the allegation that the title was misleading.

With regard to the comparative tolerability of Pradaxa vs warfarin, Boehringer Ingelheim submitted that the claim in the leavepiece, 'In RE-LY Pradaxa was generally as well tolerated as warfarin' was based upon the fact that the rate of adverse events was similar across the three treatment arms in RE-LY (Pradaxa 110mg bd, Pradaxa 150mg bd and warfarin) except for dyspepsia and GI bleeding (where rates were higher with Pradaxa). 'Any bleeding' was significantly lower with Pradaxa 150mg bd and 110mg bd compared with warfarin. Discontinuation rates in RE-LY were significantly more common for Pradaxa but the most common cause for this was 'patient decision' rather than 'poor tolerability'. Boehringer Ingelheim therefore considered that the above claim could be substantiated and that it fairly reflected the evidence. A copy of the RE-LY trial was provided.

Boehringer Ingelheim disagreed with the complainant's statement that 'major bleeding was no more frequent between the groups assigned to warfarin, dabigatran 110mg bd or 150mg bd however the higher risk of GI side effects and GI bleeding (with 150mg bd) compared with warfarin brought into question its use in people who were at risk of these effects.' In the RE-LY study, compared with warfarin, Pradaxa 150mg had similar rates of major bleeding (primary safety outcome end-point) while Pradaxa 110mg had significantly lower rates.

Boehringer Ingelheim stated that the leavepieces clearly mentioned the higher rates of GI bleeding with Pradaxa compared with warfarin. The leavepieces also clearly mentioned, as per the licensed indication and SPC, that Pradaxa 150mg bd was the recommended dose for stroke prevention in atrial fibrillation and that 110mg bd was the appropriate dose (for stroke prevention in atrial fibrillation) for patients over 80 years or taking concomitant verapamil. In certain situations (eg where thromboembolic risk was low and bleeding risk was high) a patient might need to be changed over to, or initiated on, Pradaxa 110mg bd. The leavepieces clearly stated that Pradaxa 110mg bd could also be considered for patients with gastritis, esophagitis or gastroesophageal reflux, active ulcerative GI disease or recent GI bleeding. Boehringer Ingelheim therefore considered that the presentation of the data for the use of Pradaxa in patients at high risk of bleeding was entirely appropriate.

Boehringer Ingelheim was unclear to what the complainant was referring when she stated that 'The trial only considered data for two years therefore long term safety was unclear'. There were no claims in the leavepiece about the long term safety of Pradaxa. The leavepiece only referred to the RE-LY trial upon which the licensed indication of Pradaxa was based.

With regard to what the representative said about Pradaxa, Boehringer Ingelheim submitted that within the leavepiece there was a clear and appropriate mention of the GI side effects of the medicine. It also clearly stated there was higher incidence of dyspepsia and GI bleeding with Pradaxa. In addition information on concomitant PPI use with Pradaxa, as referenced from the RE-LY trial and the SPC, was also highlighted. Boehringer Ingelheim noted that the SPC stated in Section 4.4, under haemorrhagic risk that, 'The administration of a PPI can be considered to prevent GI bleeding'. The representative had confirmed that the GI bleeding data was discussed at the meeting and in that regard her conduct was entirely appropriate.

The representative in question had confirmed that MI data was not specifically discussed at the meeting. However, although the MI rate was numerically higher with Pradaxa compared with warfarin, the increase was not significant. Boehringer Ingelheim considered that the presentation of the data on MI from the RE-LY study within the leavepieces was clear, fair and balanced, substantiated and entirely appropriate. The representative also confirmed that overall it was a very comprehensive discussion and only the certified materials were used in the meeting.

Boehringer Ingelheim stated that the representative in question had passed the ABPI Medical Representatives Exam (a copy of the certificate was provided) and had been comprehensively trained on Pradaxa and had passed a compulsory, internally validated, certified training examination on the disease area, the product and all the SPCs. This training course also included training on the use of the certified promotional materials. Boehringer Ingelheim submitted that all representatives had had to pass this examination before they were allowed to promote Pradaxa.

The representative has been with Boehringer Ingelheim for five years and three months and had always maintained high standards of professional conduct. She won the annual Boehringer Ingelheim Specialist Representative of the Year award for 2010 at the 2011 annual sales conference.

Boehringer Ingelheim stated that, as highlighted above, the Pradaxa detail aid and leavepieces and the meeting, only promoted Pradaxa in accordance with its marketing authorization. It considered that all the promotional pieces used at the meeting complied with Clause 3.2.

Boehringer Ingelheim considered that the above demonstrated that the information and claims within the detail aid and leavepieces were accurate, balanced, fair, objective and unambiguous and that these materials and the meeting itself complied with Clause 7.2. Information and claims made about side effects within the detail aid and leavepieces and the meeting reflected the available evidence and Boehringer Ingelheim considered that these materials and the meeting complied with Clause 7.9.

Boehringer Ingelheim considered that it had demonstrated above that the representative appropriately presented the certified promotional material at a legitimate meeting for health professionals. The representative maintained high standards of ethical conduct in the discharge of her duties and complied with all relevant requirements of the Code including Clause 15.2. The only material used by the representative was certified promotional material. This included an associated certified brief for how to use the material (a copy was provided). The company considered that it had complied with Clause 15.9.

Boehringer Ingelheim submitted that the meeting and promotional material used were entirely appropriate and compliant with the Code. It considered that it had maintained high standards and therefore had complied with Clause 9.1. Given the above, Boehringer Ingelheim considered that it had not brought discredit to, or reduced confidence in, the pharmaceutical industry and hence had complied with Clause 2.

PANEL RULING

The Panel noted that the leavepieces for Pradaxa 150mg and 110mg were closely similar. Each bore, on the front page, an outline lateral image of a brain: on the front half of the brain was an image of a lightening storm, on the back half was an image of an older couple riding bicycles. Superimposed in bold across the brain was the claim at issue 'Stroke Prevention'. The licensed indication appeared in full on the right hand side of the page immediately beneath the image of the brain beginning about half way down the front page. The bottom right hand corner featured the product name above the claim 'Stroke prevention in atrial fibrillation'. A red banner 'Pradaxa 110mg bd – Effective stroke reduction versus warfarin in eligible patients with an increased risk of bleeding' ran along the top of the 110mg dose leavepiece. The equivalent banner at the top of the 150mg bd leavepiece read 'Pradaxa 150mg bd – More effective stroke prevention versus warfarin in eligible patients with atrial fibrillation'. A highlighted blue triangle in the top left hand corner of each leaflet read 'New 110mg b.d.' and 'New 150mg b.d.' respectively.

The Panel noted that the licensed indication was stated in full prominently on the front page of both leavepieces and positioned such that it would be read in conjunction with the main claim 'Stroke Prevention'. Its prominence was assisted by the use of black font on a white background. The Panel considered that the full indication would be immediately obvious to readers. Given the context in which it appeared the Panel did not consider that the claim 'Stroke Prevention' on the front page of either leavepiece was misleading or inconsistent with the particulars listed in the Pradaxa SPCs as alleged. No breach of Clauses 7.2 and 3.2 was ruled. The Panel consequently ruled no breach of Clauses 9.1 and 2.

The Panel noted that both leavepieces included the prominent claim that 'In RE-LY, Pradaxa was generally as well tolerated as warfarin'. Beneath the claim was a number of bullet points and additional information.

Data from the RE-LY study (Connolly *et al* 2009) showed that the discontinuation rates for both doses of Pradaxa were statistically significantly higher at 1 year and 2 years vs warfarin ($p<0.001$). Reasons for discontinuation showed, *inter alia*, that 2.7% of patients discontinued Pradaxa (110mg and 150mg) therapy due to serious adverse events vs 1.7% of patients assigned to warfarin ($p<0.001$). GI symptoms (including pain, diarrhoea and vomiting) prompted 2.2% of patients in the Pradaxa 110mg group to discontinue therapy, 2.1% of patients in the Pradaxa 150mg group and 0.6% in the warfarin group. These differences were not statistically significant. GI bleeding resulted in the discontinuation of therapy in 1%, 1.3% and 0.9% of patients taking Pradaxa 110mg, 150mg and warfarin respectively. These differences were not statistically significant. With regard to adverse events which were reported in more than 5% of patients in any of the three treatment groups, the percentage of patients reporting each event was comparable across the groups with the exception of dyspepsia (defined to include upper abdominal pain, abdominal pain/discomfort and dyspepsia) which was reported by 11.8% of patients in the Pradaxa 110mg group, 11.3% of patients in the Pradaxa 150mg group and 5.8% of patients taking warfarin ($p<0.001$ for the comparison of either dose of Pradaxa and warfarin).

The Panel noted that discontinuation rates, rates of dyspepsia and bleeding reactions were discussed in bullet points beneath the claim at issue. These, however, were in a much smaller black font size whereas the claim at issue was separate and visually prominent in a larger, blue font. The Panel noted that it was a principle under the Code 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. The Panel thus did not consider that the claim at issue could take the benefit of the bullet points below.

The Panel considered that given the statistically significant differences between Pradaxa and warfarin with regard to dyspepsia and discontinuation of therapy because of serious adverse events, the prominent claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' did not reflect the balance of evidence and was misleading in that regard. A breach of Clauses 7.2 and 7.9 was ruled in relation to each leavepiece. These rulings were appealed.

The Panel noted that the leavepieces for Pradaxa 110mg and 150mg differed with regard to the data included about bleeding rates and so it considered each piece separately.

The leavepiece for Pradaxa 110mg included a page headed 'Rates of bleeding vs warfarin'. Beneath the heading was the prominent claim 'Significantly lower rates of any, major and life-threatening bleeding vs warfarin'. Although there were a number of bullet points beneath the claim, the Panel again

noted 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.

The Panel noted that one of the bullet points below the claim stated that GI bleeding was higher with Pradaxa 110mg but not significantly so. In that regard the Panel did not consider that the claim 'Significantly lower rates of *any*, major and life-threatening bleeding vs warfarin' (emphasis added) reflected the evidence. The claim was misleading with regard to the incidence of GI bleeding with Pradaxa 110mg vs warfarin. A breach of Clauses 7.2 and 7.9 was ruled. These rulings were appealed.

The leavepiece for Pradaxa 150mg also included a page headed 'Rates of bleeding vs warfarin'. Beneath the heading was the prominent claim 'Similar rates of major bleeding vs warfarin (primary safety outcome)'. One of the bullet points beneath the claim stated that GI bleeding was significantly higher with Pradaxa 150mg bd (warfarin, 1.07; Pradaxa 1.57: p=0.0008). The RE-LY study stated that there was a significantly higher rate of major GI bleeding with Pradaxa 150mg than with warfarin. The Panel thus considered that with regard to major GI bleeds the claim 'Similar rates of major bleeding vs warfarin (primary safety outcome)' did not reflect the balance of the data. The claim was misleading in that regard. A breach of Clauses 7.2 and 7.9 was ruled. These rulings were appealed.

The Panel noted the complainant's concern that the RE-LY study had only considered data for two years and so the long term safety was unclear. In the Panel's view neither leavepiece implied that the data presented was from a long term study. An explanation of the RE-LY study stated that patients had been followed for a median of 2 years. The Panel did not consider that the leavepieces were misleading with regard to the length of time that data had been collected. No breach of Clause 7.2 was ruled.

The Panel noted that the complainant had alleged that a representative at a meeting had glossed over GI side effects and stated that PPI cover might be required. It was also alleged that the representative did not mention the increased rate of MI with high dose Pradaxa.

The Panel noted that, in addition to the provision of the leavepieces discussed above, the representative had used the detail aid at the meeting in question. The detail aid (ref DBG 2764) was about Pradaxa 150mg. With regard to the tolerability of Pradaxa vs warfarin and the incidence of GI symptoms the Panel noted that page 8 of the detail aid was the same as that discussed above for the Pradaxa 150mg leavepiece. Thus although it was stated that rates of dyspepsia were significantly higher for Pradaxa than for warfarin (p<0.001) and that more Pradaxa patients discontinued therapy as a result of GI symptoms, this data appeared below the prominent claim 'In RE-LY Pradaxa was generally as well tolerated as warfarin'. The Panel thus considered that the claim was misleading as above and that its ruling of a breach of Clauses 7.2 and 7.9 also applied here. These rulings were appealed as above.

The Panel noted that the representatives' briefing document for page 8 of the detail aid stated that the bullet points below the claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' provided an overview of side-effects associated with Pradaxa 150mg bd. It was noted that the section provided practical guidance on managing dyspepsia (including reference to the permitted use of a concomitant PPI in the RE-LY study) and top line information about rates of MI.

The Panel noted the complainant's allegation that the representative had 'glossed over' GI side-effects. It was difficult in such circumstances to determine precisely what had been said. The dyspepsia data appeared under a heading of 'generally as well tolerated as warfarin' but the briefing material had specifically drawn the representatives' attention to the management of dyspepsia. The SPC for Pradaxa 150mg stated that the administration of a PPI could be considered to prevent GI bleeding. Although noting its rulings above, the Panel, on balance, considered that on this narrow point the briefing material was not unreasonable. No breach of Clause 15.9 was ruled.

The Panel noted its rulings above on the representatives' briefing document and detail aid. There was no way of knowing exactly what the representative had said about GI side-effects and the Panel thus ruled no breach of Clause 15.2.

The Panel noted that both parties agreed that MI data had not been discussed at the meeting. The complainant had submitted that there was an increased rate of MI with high dose Pradaxa. The Panel noted, however, that the RE-LY study, upon which the material at issue was largely based, showed that although there was an increased annual MI rate in patients taking Pradaxa 150mg vs warfarin (0.81% vs 0.64%) the difference was not statistically significant. The data from the RE-LY study regarding MI rate was included on page 8 of the detail aid and in each of the leavepieces provided to delegates. The Panel did not consider that it was necessary for representatives always to refer to all of the data given in a detail aid providing that what they did say about a medicine was not misleading or ambiguous by commission or omission. The Panel had no evidence before it to show that by not discussing the MI data the representative had given a misleading impression of the safety of Pradaxa as alleged. No breach of Clause 7.2 was ruled.

The Panel noted its rulings above and considered that overall the promotional materials at issue minimised a prescriber's concerns about the side effect profile of Pradaxa. The materials were misleading with regard to serious adverse events including major GI bleeding and also about the incidence of dyspepsia with Pradaxa. The Panel was concerned that the material had the potential to compromise patient safety. High standards had not been maintained. A breach of Clause 9.1 was ruled

which was appealed. With regard to Clause 2, which was used as a sign of particular censure, the Panel considered that providing unbalanced and misleading information about the incidence of GI bleeding and major GI bleeds was a serious matter. The materials in question were such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed.

APPEAL BY BOEHRINGER INGELHEIM

Boehringer Ingelheim noted that the materials at issue were pre-vetted and approved by the MHRA which should be considered when assessing whether they were a true representation of the data from the RE-LY study, the registration study for the extension of the product licence. Part of the function of the MHRA's pre-vetting was to ensure that the materials were factually accurate and not likely to mislead. This was especially pertinent when considering whether the materials were of a high standard (Clause 9.1) and likely to bring the industry into disrepute (Clause 2). Boehringer Ingelheim submitted that all the materials were of a high standard and their approval by the MHRA supported this.

Boehringer Ingelheim appreciated that it was very important to disclose all relevant data relating to the use of a new medicine and submitted that its materials drew attention to dyspepsia, discontinuation data and GI bleeding in a prominent way. As this data was not favourable towards Pradaxa, Boehringer Ingelheim submitted that it had been particularly open and displayed this data prominently in its materials so that prescribers were given the relevant facts to make the best decision for their patients and relate the data to their patients' individual risk: benefit profile. This did not detract from the positive data for Pradaxa, in particular reduction in the primary efficacy endpoint of the study, stroke and systemic embolism, and the primary safety endpoint, major haemorrhage, which consisted of the composite of life threatening, non life-threatening and GI bleeding (clearly defined within the RE-LY study).

Boehringer Ingelheim noted that both leavepieces (110mg and 150mg dosages) included the claim 'In RE-LY Pradaxa was generally as well tolerated as warfarin'. Table 4 in the RE-LY study summarised discontinuations, adverse events, and liver function test results. Comparing the results for either dose of Pradaxa and warfarin, a clear pattern emerged; discontinuations were higher in the Pradaxa groups than the warfarin groups, as was dyspepsia. All other comparisons between warfarin and Pradaxa were similar. The authors noted that 'The only adverse effect that was significantly more common with dabigatran than with warfarin was dyspepsia.' The RE-LY trial was not double-blind and this might have affected the discontinuation rate in the Pradaxa arms of the study, patients were more likely to be concerned by symptoms arising from the use of a new medicine (Pradaxa was not fully assessed for the new indication of stroke prevention in atrial fibrillation at that time) than an established one such as warfarin. The claim only stated that, in general, tolerability was as good as warfarin. It was therefore not incorrect. The bullet points provided further explanation to the claim by providing data on dyspepsia and discontinuation in RE-LY. Boehringer Ingelheim did not agree that the rulings of breaches of Clauses 7.2, 7.9 and especially Clauses 9.1 and 2 were appropriate when it had adopted such an open approach to sharing this data. This data was not hidden in a footnote and, although slightly smaller font was used than that in the blue sub-heading, it was prominently displayed and was immediately apparent to the reader.

Boehringer Ingelheim submitted that the aim in these materials was to clearly communicate the data from RE-LY. Boehringer Ingelheim knew it needed to prioritise safety and share clinical trial data with prescribers which was why it had claimed that Pradaxa was as well tolerated as warfarin but then listed more detailed relevant data underneath. Boehringer Ingelheim should not be penalised for being open with the data. The issue here was the heading, 'In RE-LY Pradaxa was generally as well tolerated as warfarin'. The use of the word 'tolerated' here warranted further consideration. This would be understood to be synonymous with overall safety. Major haemorrhage was the primary safety outcome of the RE-LY study and the 150mg dose of Pradaxa was associated with a similar rate of major haemorrhage to warfarin. Table 4 in Section 4.8 of the Pradaxa 150mg SPC referred to bleeding events broken down to major and any bleeding in this pivotal study. For these reasons, and because the dyspepsia rate was prominently displayed with appropriate statistical detail and referencing, it did not constitute a breach of Clauses 7.2 and 7.9.

Boehringer Ingelheim noted that the second point noted by the Panel related to the presentation of bleeding data for Pradaxa 110mg. There was omission of the gastrointestinal rates of bleeding in the heading but this data was displayed prominently underneath in the bullet points. Whilst it was understood that it was not acceptable to hide unfavourable data by the use of footnotes, this piece did not hide the data in any way, it was prominently displayed and would not be missed by the reader. Boehringer Ingelheim noted (table 5 in the Pradaxa 110mg SPC) that GI bleeding was a sub-category of major bleeding. Therefore one approach to displaying this data would have been to omit reference to GI bleeding altogether, Boehringer Ingelheim did not do this because it believed it was important that prescribers were aware of this data so they could better decide which anticoagulant would be the better choice for their patient. Definitions of the different types of bleeding were also given which was helpful for a complete understanding of the data. The Panel's ruling highlighted the word 'any' in the claim, 'Significantly lower rates of any, major and life threatening bleeding vs warfarin'. If the claim had been for significantly lower rates of 'all' bleeding (meaning all types or categories of bleeding) this would have been misleading but the word 'any' was not in breach. 'Any' referred to the sum of all bleeding. Table 5 in Section 4.8 of the SPC for

Pradaxa 110mg also included this data. In table 3 of the addendum to the RE-LY study the main categories of bleeding used in RE-LY were given which should also be considered. For all categories of bleeding the data were either the same or statistically better for Pradaxa 110mg than warfarin: the primary safety outcome of major haemorrhage was better than warfarin as was minor bleeding, major or minor bleeding, and intra-cranial bleeding; extracranial bleeding was not statistically different to warfarin. The subcategories of major bleeding were statistically better than warfarin (life threatening bleeding) or not statistically different from warfarin bleeding (non-life-threatening bleeding or gastrointestinal bleeding). Boehringer Ingelheim noted that there were many different categories of bleeding. The data for Pradaxa 110mg vs warfarin and GI bleeding was given in the leavepiece even though there was no statistical difference between the two. The relative risk of GI bleeding for Pradaxa 110mg vs warfarin was 1.08 (CI 0.85-1.38), p=0.52 (table 3, addendum). There was an 8% increase in GI bleeding with Pradaxa 110mg vs warfarin which was not statistically significant. This data was very clearly displayed. It was not usual practice to include all non-statistical results in promotional items in this way but Boehringer Ingelheim had a policy of disclosing all relevant data for prescribers and it submitted that this representation of the data reflected good practice and transparency and was not in breach of Clauses 7.2 and 7.9.

Boehringer Ingelheim noted that the third point noted by the Panel related to the leavepiece for Pradaxa 150mg and rates of bleeding. In this instance the heading was neutral, 'Rates of bleeding vs warfarin', no claim was made. The sub-heading in blue read, 'Similar rates of major bleeding vs warfarin (primary safety outcome)'. This claim could not be disputed; it was the primary safety outcome and could not be considered to be in any way misleading. In plain text bullet points underneath this sub-heading the data for any bleeding (major and minor), life threatening bleeding and gastrointestinal bleeding was given. Boehringer Ingelheim did not understand how the Panel could rule this in breach of Clauses 7.2 and 7.9. If the GI bleeding data had been omitted that would have been misleading. GI bleeding was a secondary safety outcome, albeit an important one. The sub-heading gave the primary safety outcome and other important secondary safety outcomes were listed in the bullet points, this was completely appropriate. The data regarding GI bleeding was prominently displayed and immediately obvious to the reader. It was not hidden as a footnote, there was not much text on this page, it could not be missed when looking through the leavepiece and this was Boehringer Ingelheim's intention, to accurately inform the prescriber about Pradaxa 150mg bleeding data. The balance of the data was accurately displayed and Boehringer Ingelheim strongly refuted any breach of Clauses 7.2 and 7.9.

Boehringer Ingelheim noted that the fourth area of concern expressed by the Panel was about dyspepsia in the detail aid (page 8). The Panel considered that the heading, 'In RE-LY Pradaxa was generally as well tolerated as warfarin' was misleading. Boehringer Ingelheim submitted that this was not the case because with the exception of dyspepsia, as explained above, Pradaxa 150mg was as well tolerated as warfarin. The term 'in general' meant exactly that, it did not mean tolerance of Pradaxa 150mg and warfarin were identical. In order to clarify this, the bullet points underneath addressed dyspepsia in some detail. The statement regarding tolerance was accurate in general. Because this was expanded upon for clarity, and referenced appropriately, Boehringer Ingelheim strongly refuted that this was in breach of Clauses 7.2 and 7.9 as alleged. The data regarding dyspepsia in the detail aid was extensive and detailed. Discontinuation rates were documented in addition to dyspepsia and the discontinuation rates for dyspepsia were also provided. This level of detail regarding dyspepsia demonstrated Boehringer Ingelheim's commitment to accurately communicate relevant clinical data to prescribers. The emphasis here was as much on communication of the data and education regarding Pradaxa as it was promotional. The ruling of breaches of Clauses 7.2 and 7.9 was not justified. Furthermore, Boehringer Ingelheim also provided the same advice regarding how to manage dyspepsia as used by the clinicians in the RE-LY study. This did not 'gloss over' the issue but disclosed relevant data and shared with prescribers the practical approach taken in the RE-LY study by many investigators.

Boehringer Ingelheim noted that the Panel had expressed concern about the information given on major bleeding, GI bleeding and dyspepsia and had ruled breaches of Clauses 9.1 and 2. Boehringer Ingelheim did not understand how this could be justified. Boehringer Ingelheim submitted that it had been transparent with the data and had presented any unfavourable data in detail for the benefit of the prescriber; no aspect of the data relating to bleeding or dyspepsia had been withheld or glossed over. The entire tone of the material was to promote safe and appropriate prescribing. The use of headings and sub-headings was not misleading and therefore not in breach of Clauses 7.2 and 7.9, and equally the openness and full and balanced account of the data did not justify a ruling that Boehringer Ingelheim had not maintained high standards or brought the industry into disrepute. Boehringer Ingelheim accepted that it must maintain neutral headings and not overclaim and would continue to prioritise this, so it welcomed this complaint as a means of further improving the quality of its materials, but denied breaches of Clauses 7.2, 7.9, 9.1 and 2.

COMMENTS FROM THE COMPLAINANT

The complainant noted that in a 2 year follow-up, the RE-LY study demonstrated that the lower dose of Pradaxa was non-inferior to warfarin at reducing the risk of stroke and systemic embolism in patients with atrial fibrillation.

The complainant noted that the mean rates for major bleeding were 2.71% per year for low dose Pradaxa,

3.11% per year for high dose Pradaxa and 3.36% for warfarin. Low dose Pradaxa was associated with a reduced risk of major bleeding; more patients discontinued Pradaxa than warfarin during the study – was this poor tolerability? However, the patients and doctors were aware of the treatment (Pradaxa or warfarin) therefore this might have affected the perception of side effects. There was no significant difference between the high dose Pradaxa and warfarin.

The complainant alleged that the leaflets were misleading in the light of the evidence.

The leaflet included the discontinuation due to GI symptoms below the claim that '… Pradaxa was generally as well tolerated as warfarin' and the complainant alleged this to be misleading.

The complainant alleged that with regard to monitoring, current warfarin services were a fixed cost due to existing infrastructure, therefore it seemed unlikely that there would be any real cost savings associated with the development of warfarin alternatives. For patients at high risk of stroke, warfarin was recommended although aspirin could be considered where warfarin was contraindicated. For moderate risk either warfarin or aspirin could be considered and for low risk aspirin was recommended. Potential bleeding risk must be considered in all cases where long-term anticoagulation was indicated. Plavix (clopidogrel) was not licensed for stroke prevention in patients with atrial fibrillation.

The complainant stated that in the RE-LY study serious adverse events leading to the discontinuation of Pradaxa occurred more frequently with both doses of Pradaxa (2.7%) than with warfarin (1.7%: p<0.001: number needed to harm (NNH) 100). Dyspepsia occurred in 5.8% patients on warfarin, 11.8% on 110mg Pradaxa and 11.3% 150mg Pradaxa.

APPEAL BOARD RULING

The Appeal Board noted Boehringer Ingelheim's submission that its material had been pre-vetted and approved by the MHRA. In that regard, however, the Appeal Board noted that the Code extended beyond the relevant UK legal requirements and that it and the Panel had to consider the material in the context of a complaint. Pre-vetting by the MHRA did not preclude rulings of breaches of the Code.

The Appeal Board noted that the claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' appeared in both leavepieces above a number of bullet points and additional information. The Appeal Board considered that the claim would be taken to mean that in most respects Pradaxa was as well tolerated as warfarin. In that regard readers would accept that some side-effects might occur more often with Pradaxa than warfarin (and vice versa) whereas for other side-effects there might be little difference between the medicines. The Appeal Board considered that readers would be familiar with the side-effect profile of warfarin and know that it had some problems with regard to tolerability. The Appeal Board noted the detailed information below the claim at issue, which, inter alia, referred to increased rates of discontinuation (p<0.01), dyspepsia (p<0.01) and myocardial infarction (p=ns) for Pradaxa 150mg and 110mg and considered on balance that given the context in which it appeared, the claim at issue was not misleading. The Appeal Board ruled no breach of Clauses 7.2 and 7.9 in relation to both leavepieces. The appeals on this point were thus successful.

With regard to the Pradaxa 110mg leavepiece the Appeal Board noted that the claim 'Significantly lower rates of any, major and life-threatening bleeding vs warfarin' appeared above four bullet points which gave more detailed information taken from a number of sources including the SPC. Three of the four bullet points had details of the statistically significant advantages of Pradaxa 110mg compared with warfarin for 'Any bleeding (major or minor)', 'Major bleeding' and 'Life-threatening bleeding'. The fourth bullet point stated that 'Gastrointestinal bleeding was higher with Pradaxa 110mg … but not significantly so …'. The Appeal Board was concerned that there was a difference between the ordinary use of the word 'any' and 'any' as used in the Pradaxa 110mg SPC. The Panel had taken 'any' to mean 'all' whereas 'any' in table 5 of the SPC referred to major (intracranial, GI and fatal) bleeding plus minor bleeding. In the Appeal Board's view, the meaning of 'any' in the claim at issue, was not clear but considered that, given the additional detailed information immediately below it, on balance, the claim was not misleading. No breach of Clauses 7.2 and 7.9 was ruled. The appeal on this point was successful.

With regard to the 150mg leavepiece the Appeal Board noted that the claim 'Similar rates of major bleeding vs warfarin (primary safety outcome)' was followed by three bullet points which gave more detailed information. The Appeal Board noted that from the bullet points that 'Any bleeding (major or minor)' and 'Life-threatening bleeding' were statistically significantly lower with Pradaxa 150mg compared with warfarin and 'Gastrointestinal bleeding' was statistically significantly higher with Pradaxa 150mg. The Appeal Board thus considered that, given the context in which it appeared, the claim was not misleading. No breach of Clauses 7.2 and 7.9 was ruled. The appeal on this point was thus successful.

The Appeal Board noted that page 8 of the detail aid also featured the claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' and in that regard it considered that its ruling above about the use of the claim in the leavepieces applied here. No breach of Clauses 7.2 and 7.9 was ruled. The appeal on this point was thus successful.

The Appeal Board noted its rulings above and consequently ruled no breach of Clauses 9.1 and 2. The appeal on this point was thus successful.

Complaint received **28 October 2011**

Case completed **23 February 2012**