CASE AUTH/3462/1/21

INDEPENDENT APPEAL BOARD MEMBER v BOEHRINGER INGELHEIM

Pradaxa Website

An independent member of the Code of Practice Appeal Board, complained in his capacity as a health professional, that content on the Pradaxa (dabigatran) website (pradaxa.co.uk) owned by Boehringer Ingelheim Limited was misleading and a potential risk to patient safety. The website was about the use of Pradaxa for the prevention of stroke in patients with non-valvular atrial fibrillation (NVAF).

The complainant noted that the first box of a flow chart immediately under the heading 'Simple, physician-directed dosing' stated, 'Is the patient 80 or over, or taking concomitant verapamil?' An answer of 'Yes' led straight to a box which recommended Pradaxa 110mg twice a day, morning and evening. If readers answered 'No' to the first question they were led to a box which asked them if they were worried that the patient might be at increased risk of bleeding. The arrows leading from that box pointed to a recommended dose of Pradaxa 110mg twice a day if the answer to that question was 'Yes' and to a dose of 150mg twice a day if the answer was 'No'.

The complainant was concerned that there was no box that stated that Pradaxa was contraindicated if creatinine clearance (CrCl) was <30ml/minute and no box that asked the prescriber to even consider the increased risk of bleeding in the over 80 age group.

The complainant noted that just above the flowchart was a statement about the option to prescribe a lower dose if there were concerns that a patient might have an increased risk of bleeding, but nowhere before the flowchart was it mentioned that CrCl <30ml/minute was a contraindication to the use of Pradaxa at any dose. Only in the paragraphs after the flow chart, was this contraindication mentioned, which of course might not be read if the flow chart was taken as definitive guidance.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that the homepage at issue on the Pradaxa website was headed 'Pradaxa (dabigatran etexilate) for the prevention of stroke in patients with NVAF'. Further down the homepage was the heading 'Simple, physician-directed dosing', with a statement below which referred to the flexibility of dosing, given the two doses available (110mg and 150mg), which meant that a lower dose could be prescribed if there were concerns that the patient might have an increased risk of bleeding. The flow diagram beneath this directed the prescriber to the appropriate dose of Pradaxa based on the patient's age, whether they were taking concomitant verapamil and whether they had an increased risk of bleeding. Below the flow diagram was a prominent highlighted green tab which invited readers to learn more about Pradaxa dosing and administration. Below this green tab was a shaded light blue/grey box and in italicised font were two

statements which outlined the contraindication in patients with severe renal impairment (i.e. CrCl <30ml/min) and the need to consider assessing the patient's risk of stroke, risk of bleeding and their renal function.

The Panel noted the complainant's concern that there was no box in the flow diagram that directed prescribers to consider the increased risk of bleeding in the over 80s. In that regard, the Panel noted that the flow diagram was constructed such that it recommended that patients aged 80 or over should receive a reduced dose of 110mg twice a day, which was consistent with the particulars listed in the SPC, because of the recognised increased risk of bleeding in elderly patients. The Panel thus did not consider that it was misleading not to include a box in the flow diagram to direct health professionals to consider the risk of bleeding in patients aged 80 years or over. No breach of the Code was ruled.

The Panel noted the complainant's further concern that there was no mention within or before the flow diagram that a CrCl <30ml/minute was a contraindication to the use of Pradaxa at any dose. In the Panel's view, the presentation of the statements below the diagram, in the light blue/grey box, was more akin to the provision of footnotes than being an integral part of the flow diagram. The choice of colour for the box and italicised font did not appear to suggest that the information within it was of extreme importance. This was compounded by the fact that there was a prominent green tab between the flow diagram and the italicised statements which might divert the reader's attention away from the statements before they could be read. In the Panel's view, it was not unreasonable to assume that some busy health professionals would scroll past the green button and the light blue/grey box, without realising that Pradaxa was contraindicated in patients with severe renal impairment.

Overall, the Panel considered that the provision of a flow diagram which allowed health professionals to calculate the correct dose for their patient taking into account age and bleeding risk, without clearly bringing to their attention that Pradaxa was contraindicated in severe renal impairment, was misleading. A breach of the Code was ruled.

The Panel noted its comments and ruling above and considered that high standards had not been maintained. A breach of the Code was ruled.

The Panel was particularly concerned about the placement of the statement that Pradaxa was contraindicated in patients with severe renal impairment. Many patients with non-valvular atrial fibrillation and treated with Pradaxa for the prevention of stroke were likely to be elderly and thus have some degree of renal impairment. The Panel considered that patient safety was of the utmost importance and considered that on a part of a webpage with a heading which referred to simple dosing, to have only stated that Pradaxa was contraindicated in those with severe renal impairment in what appeared to look like a footnote, was such as to reduce confidence in, and bring discredit upon, the pharmaceutical industry. A breach of Clause 2 was ruled.

An independent member of the Code of Practice Appeal Board complained in his capacity as a health professional about the Pradaxa (dabigatran) website (pradaxa.co.uk) owned by Boehringer Ingelheim Limited. The website was about the use of Pradaxa for the prevention of stroke in patients with non-valvular atrial fibrillation (NVAF).

Pradaxa was an anticoagulant indicated for the prevention and treatment of certain thrombotic conditions in adults.

COMPLAINT

The complainant alleged that the content on the current version of the pradaxa.co.uk website - Information for Health Professionals section - was misleading and a potential risk to patient safety.

The complainant noted that immediately under the heading 'Simple, physician-directed dosing' was a flow chart. The first box of the flow chart stated, 'Is the patient 80 or over, or taking concomitant verapamil?' If the answer was 'Yes' then that led straight to a box which recommended Pradaxa 110mg twice a day, morning and evening. If readers answered 'No' to the first question (ie the patient was under 80 or was not taking concomitant verapamil) they were led to a box which asked them if they were worried that the patient might be at increased risk of bleeding. The arrows leading from that box pointed to a recommended dose of Pradaxa 110mg twice a day if the answer to that question was 'Yes' and to a dose of 150mg twice a day if the answer was 'No'.

The complainant noted that there was no box that stated that Pradaxa was contraindicated if the creatinine clearance was below 30ml/minute and, of concern, no box that asked the prescriber to even consider the increased risk of bleeding in the over 80 age group.

The complainant noted that just above the flowchart was a statement to the effect that there was the option of prescribing a lower dose if there were concerns that a patient might have an increased risk of bleeding - but nowhere before the flowchart was it mentioned that a creatinine clearance of less than 30ml/minute was a contraindication to the use of Pradaxa at any dose. Only in the paragraphs after the flow chart, was this contraindication mentioned - which of course might not be read if the flow chart was taken as definitive guidance.

The complainant stated that his/her particular concern was around the 10% or more prevalence of stages 3-5 chronic kidney disease in the 80+ age group, which was often undetected and symptomless (Hallan et al 2016).

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

RESPONSE

Boehringer Ingelheim stated that, based on the complainant's description, the material in question was the home page of the Pradaxa.co.uk website (ref PC-GB-100765 V1) which was specifically for access by health professionals.

Boehringer Ingelheim did not consider that the material was in breach of Clause 7.2 'Information, Claims and Comparisons', as when viewed in context, it included all relevant information, and was presented in a manner consistent with the Pradaxa summary of product characteristics (SPC) for the 110mg and 150mg formulations.

Boehringer Ingelheim noted that the complaint was about an excerpt of the Pradaxa website homepage, a diagram that was used to explain the dose reduction criteria for Pradaxa; the complainant had not included the context in which the diagram appeared. Boehringer Ingelheim submitted that when viewed in context, the diagram was clearly accompanied by a statement directly below it that included the wording 'Pradaxa is contraindicated in patients with severe renal impairment (i.e. CrCl <30ml/min)'. That statement was an integral part of the piece, included in the same size font as the rest of the material, and was highlighted in a blue call out box directly below the diagram, drawing attention to it. This placement of the renal contraindication after the diagram summarising the dosing criteria was consistent with the layout of the same information in Section 4.2 of the Pradaxa SPC.

Boehringer Ingelheim noted that in Section 4.2 'Posology and method of administration', the SPCs first presented 'dose reduction recommended' to 110mg twice a day in relation to:

- age (patients aged 80 years or over)
- or those receiving concomitant verapamil, a known drug-drug interaction that was specifically mentioned in the SPC (which increased dabigatran plasma concentrations and therefore the risk of bleeding)

and then 'dose reduction for consideration', based on an individual assessment of bleeding risk. Boehringer Ingelheim noted that the following dose recommendation table appeared in the Pradaxa SPCs:

Dose recommendation table for stroke prevention in non-valvular atrial fibrillation
(Pradaxa 110mg SPC, dated 14 May 2020, Pradaxa 150mg SPC, dated 14 May 2020)

	Dose recommendation
Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (SPAF)	300 mg Pradaxa taken as one 150 mg capsule twice daily
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE)	300 mg Pradaxa taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days
Dose reduction recommended	
Patients aged ≥80 years	daily dose of 220 mg Pradaxa taken as one 110 mg capsule twice daily
Patients who receive concomitant verapamil	
Dose reduction for consideration	
Patients between 75-80 years	daily dose of Pradaxa of 300 mg or 220 mg should be selected based on an individual assessment of the
Patients with moderate renal impairment (creatinine clearance 30-50 mL/min)	

	Patients with gastritis, esophagitis or gastroesophageal reflux	thromboembolic risk and the risk of bleeding
	Other patients at increased risk of bleeding	

Only after that dose recommendation table did the SPC address the need to assess renal function prior to and during Pradaxa treatment, and where a statement was included related to Pradaxa being contraindicated in patients with severe renal impairment (creatinine clearance <30ml/min).

Boehringer Ingelheim noted the complainant's concern that there was no box within the dose reduction flow chart to consider whether there was an increased risk of bleeding in patients over 80 years. That was due to a dose reduction being recommended in the SPC for *all* eligible patients aged 80 years or above, due to the recognised increased risk of bleeding in that population.

Boehringer Ingelheim stated that the purpose of the material was purely to support health professionals with choice of the appropriate dose of Pradaxa, in line with the SPC; it was not intended to be a decision tree for initiating prescription overall. The diagram therefore focussed on the patient characteristics that were specifically related to dose reduction. It was accompanied prominently by the following statement which highlighted the need to consider broader patient characteristics before determining the patient's suitability for Pradaxa:

> 'Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment. Pradaxa is contraindicated in patients with severe renal impairment (i.e. CrCL <30ml/min). Prior to prescribing Pradaxa please ensure that you have assessed the patient's risk of stroke, risk of bleeding and their renal function. These will help you determine the patient's suitability for Pradaxa and the appropriate dose for them.'

Boehringer Ingelheim noted that between the diagram and the blue call out box referred to above, there was a green button 'Learn more about Pradaxa Dosing and Administration', which led health professionals to a Dosing and Administration page where more comprehensive details were provided in order to support the health professional in selecting the most appropriate patient for Pradaxa and then also selecting the correct dose, based on the patient's characteristics.

Boehringer Ingelheim, however, always appreciated the opportunity to review its materials in light of feedback from whatever source and stated that it put patient safety and compliance with the Code at the forefront of all activities. Upon receipt of the complaint, the relevant team members met the next working day and removed the material from the website whilst the company reviewed the matter. Boehringer Ingelheim intended to reinstate the material in due course, but with an adjustment to move the renal function statement to above the diagram. Whilst this was no longer in line with the SPC presentation (though it was with the content), Boehringer Ingelheim hoped it addressed the feedback of the complainant.

In conclusion, for the reasons stated above, Boehringer Ingelheim did not consider that it had breached Clauses 2, 7.2 or 9.1 of the Code as its material was consistent with the SPCs in both content and presentation of dosing.

PANEL RULING

The Panel noted that the homepage at issue on the Pradaxa website was headed 'Pradaxa (dabigatran etexilate) for the prevention of stroke in patients with NVAF'. The homepage included, *inter alia*, information about the medicine's mechanism of action and cost savings relative to other oral anticoagulants of the same type. Further down the homepage was the heading 'Simple, physician-directed dosing', with a statement below which referred to the flexibility of dosing, given the two doses available (110mg and 150mg), which meant that a lower dose could be prescribed if the health professional was concerned that the patient might have an increased risk of bleeding. The flow diagram beneath this directed the prescriber to the appropriate dose of Pradaxa based on the patient's age, whether they were taking concomitant verapamil and whether they had an increased risk of bleeding. Below the flow diagram was a prominent highlighted green tab which invited readers to learn more about Pradaxa dosing and administration. Below this green tab was a shaded light blue/grey box and in italicised font were two statements. The first statement provided examples of the patients who might be at increased risk of bleeding, while the second statement read:

> 'Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment. Pradaxa is contraindicated in patients with severe renal impairment (i.e. CrCL < 30ml/min). Prior to prescribing Pradaxa please ensure that you have assessed the patient's risk of stroke, risk of bleeding and their renal function. These will help you determine the patient's suitability for Pradaxa and the appropriate dose for them.'

The Panel noted the complainant's concern that there was no box in the flow diagram that directed the prescriber to consider the increased risk of bleeding in the over 80 age group. In that regard, the Panel noted that if patients were at an increased risk of bleeding, then the dose of Pradaxa should be reduced. The flow diagram was constructed such that it recommended that patients aged 80 or over should receive a reduced dose of 110mg twice a day. This was consistent with the particulars listed in the Pradaxa 110mg SPC which, because of the recognised increased risk of bleeding in elderly patients, stated that a dose reduction for all patients aged 80 or over was recommended. The Panel thus did not consider that it was misleading not to include a box in the flow diagram to direct health professionals to consider the risk of bleeding in patients aged 80 years or over. No breach of Clause 7.2 was ruled.

The Panel noted the complainant's further concern that there was no mention within or before the flow diagram that a creatinine clearance below 30ml/minute was a contraindication to the use of Pradaxa at any dose. The Panel considered the content and layout of the flow diagram and the information around it. The Panel considered the immediate and overall impression to a busy health professional.

In the Panel's view, the presentation of the statements below the diagram, in the light blue/grey box, was more akin to the provision of footnotes than being an integral part of the flow diagram. The choice of colour for the box and italicised font did not appear to suggest that the information within it was of extreme importance. This was compounded by the fact that there was a prominent green tab between the flow diagram and the italicised statements which might divert

the reader's attention away from the statements before they could be read. Although the prominent green tab invited the reader to learn more about the dosing and administration of Pradaxa, that information was only available if the button was 'clicked'. In the Panel's view, it was not unreasonable to assume that some busy health professionals would scroll past the green button and the light blue/grey box, without realising that Pradaxa was contraindicated in patients with severe renal impairment.

The Panel noted Boehringer Ingelheim's submission that the placement of the renal contraindication after the flow diagram, which summarised the dosing criteria, was consistent with the layout of the same information in Section 4.2 of the Pradaxa SPC. In that regard, however, the Panel noted that the layout of an SPC followed a standard format as it was a regulatory document; the material at issue was a promotional website and had to comply with the Code. The Panel further noted that the layout of Section 4.2 of the Pradaxa SPC was different in the 110mg and the 150mg SPCs.

Section 4.2 of the Pradaxa 110mg SPC stated, inter alia, 'In all patients and especially in the elderly (>75 years), as renal impairment may be frequent in this age group: Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 mL/min) (see sections 4.3, 4.4 and 5.2). The Panel noted that this information was placed in the 110mg SPC before the information about dose recommendations for the prevention of stroke in patients with NVAF.

Overall, the Panel considered that the provision of a flow diagram which allowed health professionals to calculate the correct dose for their patient taking into account age and bleeding risk, without clearly bringing to their attention that Pradaxa was contraindicated in patients with severe renal impairment, was misleading. A breach of Clause 7.2 was ruled.

The Panel noted its comments and ruling above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel was particularly concerned about the placement of the statement that Pradaxa was contraindicated in patients with severe renal impairment. Many patients with non-valvular atrial fibrillation and treated with Pradaxa for the prevention of stroke were likely to be elderly and thus have some degree of renal impairment. The flow diagram incorrectly implied that prescribers needed only to 'select the most appropriate dose' after assessing patients according to age, concomitant verapamil and risk of bleeding and in that regard, the Panel considered that there was a risk that some patients with severe renal impairment, for which Pradaxa was contraindicated, might be inappropriately treated with Pradaxa. The Panel considered that patient safety was of the utmost importance and considered that on a part of a webpage with a heading which referred to simple dosing, to have only stated that Pradaxa was contraindicated in those with severe renal impairment in what appeared to look like a footnote, was such as to reduce confidence in, and bring discredit upon, the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **27 January 2021**

Case completed **3 August 2021**