PRESCRIBING ADVISOR v BOEHRINGER INGELHEIM

Promotion of Pradaxa

A prescribing advisor alleged that Boehringer Ingelheim had promoted unlicensed doses of Pradaxa (dabigatran) in breach of the Code.

The use of Pradaxa had been restricted to the orthopaedic unit at the complainant's local hospital. The complainant provided a copy of a letter, dated October 2009 and signed by three consultant orthopaedic surgeons, which stated:

> **'In orthopaedics, as you know, for years we have used Enoxaparin 20. Recently we converted to Pradaxa and have had a significant number of leaky orthopaedic wounds and 2 rectal bleeds.**
>
> **On unofficial advice from Pradaxa reps we reduced Pradaxa to half dosage, however this is unlicensed'.**

The detailed response from Boehringer Ingelheim is given below. It was sent to the complainant for comment prior to the Panel making a ruling.

The Panel noted that the recommended dose of Pradaxa was 220mg daily taken as 2 capsules of 110mg. Treatment should be initiated orally within 1-4 hours of completed surgery (total hip or knee replacement) with a single capsule. Two capsules were to be given thereafter once daily for a total of 10 days.

The Panel noted the complainant's statement that 'several consultant surgeons contacted the company' apparently as a result of a number of patients developing bleeds whilst on Pradaxa. The letter, signed by three consultant orthopaedic surgeons, and referred to above, gave no details to identify the 'Pradaxa reps'; it was not known where, when or in what context information about the apparent routine use of half doses of Pradaxa had been given nor was it certain if the consultants' use of 'reps' meant medical (sales) representatives or someone else representing Boehringer Ingelheim. It was not known if the information had been provided in response to an unsolicited enquiry, although this was unlikely given that there was no record to show that it had been via Boehringer Ingelheim's medical information department.

Boehringer Ingelheim did not know which consultants had signed the letter of 20 October. Neither of the two medical representatives who covered the hospital at issue had discussed the use of half dose Pradaxa with the orthopaedic staff. As part of a discussion about bleeds in a patient aged over 75, representative one had discussed the use of a reduced dose of Pradaxa in patients in that age group (150mg/day vs 220mg/day). That representative had not covered the hospital after July 2009. The representative responsible for the hospital after that date had not discussed the use of half doses of Pradaxa and, when the complaint was received, had had little contact with the orthopaedic department.

Representatives' briefing material clearly stated that Pradaxa had two fixed doses – a standard dose (220mg/day) and a lower dose (150mg/day) for special patient populations. Promotional material similarly referred to these two doses. The Panel was concerned to note, however, that in May 2009 the sales force was briefed about inter-company correspondence in which a competitor had asserted that the Pradaxa field force had promoted choice and flexibility of dose. Representatives had been reminded to promote 220mg as the main dose of Pradaxa and that the 150mg dose continued to be discussed within the context of special patient populations.

On the basis of the evidence before it, the Panel considered that it was impossible to know what had transpired. The complainant had the burden of proving their complaint on the balance of probabilities. It seemed clear that the consultants had discussed half dose Pradaxa with someone from Boehringer Ingelheim whose identity was not known, neither was the context in which the conversation had taken place known. However both parties assumed that it was likely to have been sales representatives. A lower dose was licensed for special patient populations. Half dose Pradaxa, except within four hours of surgery, was unlicensed. This was not the first time it had been asserted that Boehringer Ingelheim representatives had promoted unlicensed doses. A judgement had to be made on the available evidence in the present case bearing in mind the extreme dissatisfaction usually necessary on the part of an individual before he or she was moved to submit a complaint. The Panel was very concerned about the matter. On balance, it considered that on the basis of the evidence provided by the parties the circumstances were such that breaches of the Code could not be ruled.

Following its consideration of this complaint the Panel considered that Boehringer Ingelheim would be well advised to remind its representatives of the need to be extremely clear about the dose of Pradaxa.

A prescribing advisor complained about the promotion of Pradaxa (dabigatran) by Boehringer Ingelheim Limited.

COMPLAINT

The complainant noted that Pradaxa was approved for use for its licensed indications and at licensed doses in summer 2008. Its use had been restricted to the orthopaedic unit at the complainant's local hospital. It was noted since approval that a number of patients developed bleeds whilst on this medicine. Several consultant surgeons contacted the company whose representatives advised them 'unofficially' that it could be used at 'half dose'. The consultants had not sought the advice of the hospital pharmacy medicines information department. The complainant had a letter from the consultants confirming the above; the letter was subsequently provided in response to a request from the Authority. The letter, dated 20 October 2009 and headed 'DVT prophylaxis', began:

> 'In orthopaedics, as you know, for years we have used Enoxaparin 20. Recently we converted to Pradaxa and have had a significant number of leaky orthopaedic wounds and 2 rectal bleeds.
>
> On unofficial advice from Pradaxa reps we reduced Pradaxa to half dosage, however this is unlicensed'.

The complainant alleged that the advice to use Pradaxa at an unlicensed dose might be in breach of the Code.

When writing to Boehringer Ingelheim the Authority asked it to respond in relation to the requirements of Clauses 3.2, 15.2 and 15.9 of the Code.

RESPONSE

Boehringer Ingelheim emphasised that it was committed to operating in a responsible, ethical and professional manner and it strove through its activities and materials to maintain high standards and strengthen the image of the pharmaceutical industry. Therefore, it was surprised and disappointed to have received the complaint which related to the conduct of its field force.

Boehringer Ingelheim understood that an anonymous consultant orthopaedic surgeon at a named hospital claimed to have contacted an undisclosed number of Boehringer Ingelheim representatives for advice about a problem with some of his patients rather than approaching the hospital's medicines information department for advice. In the consultant's view, the advice received recommended the use of Pradaxa at an unlicensed dose. The complaint was from another anonymous employee of the same hospital.

Boehringer Ingelheim submitted that it was not clear from the letter when and where the alleged 'off-label' advice was given by its representative and without further information from the complainant it was difficult to investigate the allegations completely. However, Boehringer Ingelheim had investigated the matter thoroughly given the information provided.

Boehringer Ingelheim submitted that since the launch of Pradaxa in April 2008 there had been no medical information requests from the hospital in question and therefore it assumed that the complaint related to its representative specifically responsible for that hospital. Two representatives had covered the hospital (representative 1 until 1 July 2009; representative 2 after 1 July 2009). Each representative had been asked about their communication and contact with any health professionals at the hospital during their work.

Representative 1

- April 2009: met an orthopaedic consultant and presented to the pharmacy department when the correct dosing regime for Pradaxa was clarified.
- May 2009: met three consultants in anaesthetics. Also met another to discuss orthopaedic nurse training. During this meeting the representative was informed of a bleed with Pradaxa at the higher licensed dose in patient over the age of 75. The representative immediately communicated the correct dosing regime with all key personnel. The summary of products characteristics (SPC) stated 'In elderly patients (>75 years) there is limited clinical experience. The patients should be treated with caution. The recommended dose is 150mg taken once daily as 2 capsules of 75mg (see Section 4.4 and 5.1)'.
- The representative did not state that half dosing for Pradaxa could be used.
- No medical information requests were received following on from these calls.

Representative 2

- July 2009: met one orthopaedic consultant but did not discuss halving the dose of Pradaxa
- The orthopaedic department cancelled a meeting scheduled for November 2009.
- Since the meeting in July the representative had had no communication with the department.
- The representative had never been in face-to-face communication with the hospital's pharmacy; however, Pradaxa patient information cards and Pradaxa dosing cards were left upon request.

Boehringer Ingelheim submitted that orthopaedic consultants from the hospital attended the British Orthopaedic Association Annual Conference in September 2009, however there was no record of any medical information request on the dosing of Pradaxa from them. The consultant's letter appeared to have been written after this conference.

Boehringer Ingelheim stated that its representatives had acted with the highest standard of ethical conduct in the discharge of their duties and therefore complied with all relevant requirements of the Code. Boehringer Ingelheim therefore submitted that it was not in breach of Clause 15.2.

Boehringer Ingelheim submitted that its representative training and briefing materials clearly did not advocate any course of action which would be likely to be a breach of the Code. Neither the current Pradaxa detail aid nor its briefing for use referred to the licensed use of a half dose of Pradaxa, except on the day of surgery for its initial dose. Similarly the scientific support aid for representatives' use during calls did not refer to the licensed use of a half dose of Pradaxa, except on the day of surgery for its initial dose.

Boehringer Ingelheim submitted that it had never produced material that referred to a lower than usual dose of Pradaxa.

Boehringer Ingelheim provided a copy of the representatives' briefing material about how to handle 'off-label' enquiries, this was included in a proactive briefing to the representatives covering a press release of results of a clinical trial for an 'off-label' indication.

Boehringer Ingelheim also provided a copy of the email which covered a briefing that was sent to its sales team to clarify that its promotional materials, training and activities were consistent with the SPC.

Boehringer Ingelheim submitted that the materials and briefings provided clearly complied with the relevant requirements of the Code and did not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. Therefore, Boehringer Ingelheim denied a breach of Clause 15.9.

Boehringer Ingelheim further submitted that it had clearly demonstrated by the materials and briefings provided, and the conduct of its representatives, that the promotion of Pradaxa had been within the terms of the marketing authorization and consistent with the SPC. The company thus denied a breach of Clause 3.2.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant did not have any more information on the details of the advice ie who gave it and when. The complainant considered, however, that it must have been Boehringer Ingelheim sales staff and that they and their superiors must take ownership for it. The end result was that a significant portion of very vulnerable post total hip and total knee replacement patients were exposed to an unnecessary health risk by being discharged from hospital on sub-therapeutic treatment. The consequences of venous thromboembolism, both clinically diagnosed and un-diagnosed were poorly recognised and this advice exposed patients to risks that they did not deserve. Pradaxa was aggressively marketed locally and it was disappointing that Boehringer Ingelheim would not take ownership of poor advice from its representatives.

PANEL RULING

The Panel noted that the recommended dose of Pradaxa was 220mg daily taken as 2 capsules of 110mg. Treatment should be initiated orally within 1-4 hours of completed surgery (total hip or knee replacement) with a single capsule. Two capsules were to be given thereafter once daily for a total of 10 days.

The Panel noted the complainant's statement that 'several consultant surgeons contacted the company' apparently as a result of a number of patients developing bleeds whilst on Pradaxa. The complainant had provided a copy of a letter, dated 20 October 2009 and signed by three consultant orthopaedic surgeons, which stated 'On unofficial advice from Pradaxa reps we reduced Pradaxa to half dosage, however this is unlicensed'. No details had been provided to identify the 'Pradaxa reps'; it was not known where, when or in what context information about the apparent routine use of half doses of Pradaxa had been given nor was it certain if the consultants' use of 'reps' meant medical (sales) representatives or someone else representing Boehringer Ingelheim. It was not known if the information had been provided in response to an unsolicited enquiry, although this was unlikely given that there was no record to show that it had been via Boehringer Ingelheim's medical information department.

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Following its consideration of this complaint the Panel considered that Boehringer Ingelheim would be well advised to remind its representatives of the need to be extremely clear about the dose of Pradaxa.

Complaint received **26 November 2009**

Case completed **29 April 2010**