CASE AUTH/2357/9/10

# GENERAL PRACTITIONER v BOEHRINGER INGELHEIM

## Promotion of Pradaxa

**A general practitioner complained that an advertisement for Pradaxa (dabigatran), issued by Boehringer Ingelheim, included a claim for therapeutic equivalence with enoxaparin based on non-inferiority studies. To claim equivalence on the basis of such studies was misleading, exaggerated the facts, could not be substantiated and endangered patients safety. Non-inferiority was not the same as comparability. The complainant alleged that the claims in question implied a possible superiority of Pradaxa vs enoxaparin with regard to safety and efficacy. The complainant alleged that the general reference to safety in the claims was misleading as it implied that the safety profile of Pradaxa was equivalent/comparable to enoxaparin which was not so. The complainant also noted that the claims did not specify the dose of enoxaparin which suggested that Pradaxa was equivalent to any dose of enoxaparin which was not so, as shown in the RE-MOBILIZE study. The complainant further noted that the RE-MOBILIZE study, which failed to show non-inferiority vs enoxaparin, had not been cited by Boehringer Ingelheim and in this regard the complainant alleged that the company had cherry-picked the data. This misled clinicians as to the evidence base supporting the claims.**

**In addition to the advertisement, the complaint also referred to the activity of sales representatives.**

**The detailed response from Boehringer Ingelheim is given below.**

**The Panel noted that the advertisement at issue featured the claim 'Well balanced' beneath a depiction of a set of balanced scales. Beneath 'Well balanced' was the claim 'Once-daily, oral anticoagulation Efficacy and safety equivalent to enoxaparin in primary prevention of VTE [venous thromboembolism] after total knee or hip replacement surgery'. This claim was referenced to Eriksson *et al*, (2007a) (RE-NOVATE study) and Eriksson *et al*, (2007b) (RE-MODEL study). Both studies were non-inferiority studies to compare the efficacy and safety of Pradaxa with enoxaparin after total hip or total knee replacement respectively. The Panel noted that non-inferiority studies showed that even if one medicine was not as good as another, the difference between the two was not clinically important.**

**The Panel rejected the complainant's allegation that the claim in question implied a possible superiority of Pradaxa vs enoxaparin. Nonetheless the claim, together with the perfectly balanced scales, implied that Pradaxa had been shown to be unequivocally equivalent to enoxaparin and that was not so. In that regard the Panel considered that the claim was misleading and could not be substantiated. Breaches of the Code were ruled as accepted by Boehringer Ingelheim. The Panel further considered that the claim did not reflect the available evidence about the safety of Pradaxa. A further breach of the Code was ruled.**

**In the Panel's view the advertisement would be read in the context of the licenced doses of Pradaxa and enoxaparin after total knee or hip replacement surgery. The Panel did not accept that because the claim did not state the dose of enoxaparin that it implied that Pradaxa had been shown to be equivalent to any dose of enoxaparin. The Panel did not consider that the claim at issue was misleading in this regard and no breach of the Code was ruled. Upon appeal by the complainant, the Appeal Board considered that it was good practice to include the relevant dosage particulars in claims about medicines. Nonetheless, given the tightly defined dose of enoxaparin in the prevention of VTE after total hip or knee replacement surgery, the Appeal Board did not consider that it was misleading not to have stated the dose in the advertisement and it upheld the Panel's rulings of no breach of the Code.**

**The Panel further noted the allegation that by not referring to the RE-MOBILIZE study, Boehringer Ingelheim had 'cherry-picked' the data. The RE-MOBILIZE study had used a lower dose of enoxaparin ie 30mg/day, than that licensed in the UK for the prevention of VTE following total knee or hip replacement surgery ie 40mg/day. In that regard the Panel did not consider that the claim misled clinicians as to the evidence base to support the claim at issue as alleged. No breach of the Code was ruled. Upon appeal by the complainant the Appeal Board noted that the RE-MOBILIZE study had used enoxaparin 30mg twice daily ie a higher dose than that licensed in the UK. The Appeal Board considered that as the RE-MOBILIZE study had used a dose of enoxaparin not licensed in the UK, and therefore not relevant to UK prescribers, it was not misleading not to include the study in the evidence base to support the comparative claim at issue. The Appeal Board upheld the Panel's ruling of no breach of the Code.**

**With regard to the activities of sales representatives the Panel noted that the complainant had not made any specific allegations. The front page of the detail aid was visually similar to the advertisement. However, below the depiction of the scale pans was the claim 'Once-daily oral anticoagulation Efficacy and safety *comparable* to enoxaparin' (emphasis added). The claim was referenced to the RE-NOVATE and RE-MODEL studies. Throughout the detail aid Pradaxa and enoxaparin were variously described as being**

**'comparable' or 'similar'. The detail aid did not describe the two medicines as equivalent. The briefing notes for representatives referred to the comparability of Pradaxa to enoxaparin – not to their equivalence. The Panel did not consider that comparability implied equivalence – comparable only meant that the two products were able to be compared. The Panel did not consider that the material used by the representatives was misleading as alleged. No breach of the Code was ruled. Upon appeal by the complainant the Appeal Board did not consider, given the common understanding of comparable, that the detail aid was misleading as alleged. The Panel's ruling was upheld.**

**The Panel noted its rulings above and did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure. The Panel's ruling of no breach was upheld on appeal.**

A general practitioner complained about the promotion of Paradaxa (dabigatran) by Boehringer Ingelheim Limited. The material at issue was an advertisement (ref DGB1729b) which was published in The Pharmaceutical Journal, 18 September 2010. The complainant also referred to the activity of sales representatives.

Pradaxa was indicated for primary prevention of venous thromboembolic events in adult patients who had undergone elective total hip replacement surgery or total knee replacement surgery.

## COMPLAINT

The complainant noted that the advertisement at issue featured claims that Pradaxa was well balanced and that its efficacy and safety was equivalent to enoxaparin in the primary prevention of venous thromboembolism (VTE) after total knee or hip replacement surgery.

The complainant submitted that this claim of therapeutic equivalence, based on results derived from studies which employed a non-inferiority study design, appeared to be at odds with the clear and unambiguous ruling in Case AUTH/2270/10/09. Review of the two references cited as substantiation for these claims (Eriksson *et al*, 2007a (RE-NOVATE study) and Eriksson *et al*, 2007b (RE-MODEL study)), and the ruling in Case AUTH/2270/10/09 indicated that the only claim supported by these studies was that Pradaxa was non-inferior to enoxaparin. To suggest apparent equivalence to enoxaparin clearly exaggerated the facts, could not be substantiated and importantly endangered patient safety. There really was a difference between showing non-inferiority and showing comparability and Boehringer Ingelheim had conveniently ignored this salient fact. The claims in question implied a possible superiority of Pradaxa vs enoxaparin with regard to its efficacy and safety.

The complainant referred to some relevant background information on the RE-NOVATE, RE-MODEL and RE-MOBILIZE studies reported in a review regarding the evidence base for Pradaxa vs enoxaparin and that none of the studies supported a claim of equivalence or superiority (Weitz 2010). The complainant reproduced a table of data from Weitz.

The complainant was also concerned that the generalisations employed were misleading and potentially endangered patient safety. Firstly, the general reference to safety in the claims was misleading as it implied that the safety profile of Pradaxa was entirely equivalent/comparable to enoxaparin; this was not so given that the studies cited focused on bleeding outcomes and other specified thromboembolic outcomes as primary and secondary outcomes and that the hepatic and cardiac safety profiles, amongst other things, of these two medicines were not equivalent or comparable. Secondly, the clinical studies comparing Pradaxa with enoxaparin used differing doses of enoxaparin, as was the case in clinical practice. The claims did not specify the dosage of enoxaparin and so suggested that Pradaxa had been proven to be equivalent (or correctly, non-inferior) to any dose of enoxaparin; this was not so as shown by the not insignificant Phase 3 trial RE-MOBILIZE which used enoxaparin 30mg twice daily (instead of 40mg once daily) and importantly also failed to achieve non-inferiority vs enoxaparin. Thirdly, the latter clearly indicated that Boehringer Ingelheim had cherry-picked the data and referred only to those studies where non-inferiority vs enoxaparin had been achieved; this misled clinicians as to the evidence-base supporting these claims.

When writing to Boehringer Ingelheim the Authority asked it to respond in relation to Clauses 2, 7.2, 7.3, 7.4, 7.9 and 7.10, of the Code of Practice.

## RESPONSE

Boehringer Ingelheim noted that the two principal clinical studies supporting the marketing authorization for the efficacy and safety of dabigatran in the EU employed a non-inferiority study design. Both studies, the RE-NOVATE study in total hip replacement and the RE-MODEL study in total knee replacement, demonstrated non-inferiority to enoxaparin in the prevention of major VTE and VTE-related mortality during treatment (the primary variable). There were no significant differences between dabigatran and enoxaparin on any safety parameters.

Each study compared the efficacy and safety of two doses of dabigatran, both of which had since received marketing approval, compared with enoxaparin. More detailed review of the results showed that at the higher approved dose of dabigatran (220mg) VTE was numerically lower than enoxaparin but major bleeding events were numerically higher although no differences achieved statistical significance. At the lower approved dose of dabigatran (150mg) VTE was numerically a little higher and bleeding events

numerically lower than enoxaparin again with no statistically significant differences. These results were reflected in the table of data from Weitz provided by the complainant. With regard to other adverse events the profiles of dabigatran and enoxaparin were very similar as reflected in the unwanted effects section of the Pradaxa summary of product characteristics (SPC).

Boehringer Ingelheim noted the allegation that the claims in question implied a possible superiority of Pradaxa vs enoxaparin with regard to its efficacy and safety and the complainant's reference to Case AUTH/2270/10/09 to support his position. Case AUTH/2270/10/09 referred to the claim 'at least as effective as…' which was ruled to imply superiority. Boehringer Ingelheim believed that this claim fundamentally differed from the claim 'equivalent to' which did not imply any degree of superiority (since it could only imply equivalence) and so strongly refuted the allegation of implied superiority.

Boehringer Ingelheim accepted that the data did not substantiate the claim of 'equivalent efficacy to enoxaparin'. Indeed this was accepted and fully reflected in earlier Pradaxa promotional materials where the corresponding claims referred to 'comparable' efficacy and safety profiles. Further investigation of the preparation and approval of the advertisement with regard to the change of wording was an oversight and not rejected during the approval process.

Boehringer Ingelheim agreed that the advertisement was in breach of Clauses 7.2, 7.3, 7.4 and 7.10, and had since rigorously reviewed its internal approval processes to ensure that this anomaly could not occur again.

Boehringer Ingelheim noted that the complainant also alleged that the company had 'cherry picked the data' as the RE-MOBILIZE study was not presented. The complainant surmised that the absence of information on the RE-MOBILIZE study might be because the study failed to demonstrate non-inferiority to a standard US regimen of enoxaparin. The RE-MOBILIZE study was not normally referred to in any UK, or indeed EU materials and was not referred to in the SPC as the study was designed for the US with a regimen for enoxaparin (30mg twice daily) which was fairly specific to that region and different from the standard EU regimen of 40mg once daily. The study did not demonstrate non-inferiority, possibly due to the higher dose regimen of enoxaparin. Omission of this study was not 'cherry picking', it was simply that the study covered a dosing regimen not commonly used in the UK, or Europe.

Boehringer Ingelheim noted the allegation that the 'general reference to safety … was misleading as it implied that the safety profile of Pradaxa was entirely equivalent/comparable to enoxaparin'. The materials in question referred to 'Well balanced combination of efficacy and safety', 'A safety profile comparable to enoxaparin after total hip or knee replacement' and 'VTE prevention comparable to enoxaparin after total hip or knee replacement'. Boehringer Ingelheim noted that it made no claim or implication of equivalence as alleged. Furthermore, Boehringer Ingelheim considered that these statements were appropriate and consistent with the data.

Any form of anticoagulation was subject to link between the level of anticoagulation which would affect efficacy and the associated risk of bleeding events (safety). In clinical studies, both licensed doses of Pradaxa had demonstrated non-inferiority to the current 'gold standard therapy' with a very similar incidence of bleeding events and a similar overall adverse event profile.

Boehringer Ingelheim submitted that data provided in the Pradaxa SPC illustrated these findings and fully substantiated claims of comparable efficacy and a comparable safety profile to enoxaparin. Importantly, the cardiac and hepatic safety profiles were specifically studied in the clinical trials and there was no evidence of important differences as alleged by the complainant.

Although not the subject of any specific aspect of the complaint, Boehringer Ingelheim provided copies of the detail aid and associated briefing material.

In response to a request for further information Boehringer Ingelheim stated that The Pharmaceutical Journal did not contain any other information about Pradaxa aside from the advertisement in question. Boehringer Ingelheim submitted that it was not clear which aspect of the sales representatives' activities was referred to by the complainant. In the absence of this additional information Boehringer Ingelheim did not believe it needed to comment further on Clauses 2, 7.2, 7.3, 7.4, 7.9 or 7.10.

## PANEL RULING

The Panel noted that the advertisement at issue featured the claim 'Well balanced' beneath a depiction of a set of balance scales with the two pans, one red, one blue exactly balanced. Beneath 'Well balanced' was the claim 'Once-daily, oral anticoagulation Efficacy and safety equivalent to enoxaparin in primary prevention of VTE after total knee or hip replacement surgery'. This claim was referenced to Eriksson *et al*, (2007a) (RE-NOVATE study) and Eriksson *et al*, (2007b) (RE-MODEL study). Both studies were non-inferiority studies to compare the efficacy and safety of Pradaxa with enoxaparin after total hip or total knee replacement respectively. The Panel noted that non-inferiority studies showed that even if one medicine was not as good as another, the difference between the two was not clinically important.

The Panel rejected the complainant's allegation that the claim in question implied a possible superiority of Pradaxa vs enoxaparin. Nonetheless the claim, together with the perfectly balanced scales, implied

that Pradaxa had been shown to be unequivocally equivalent to enoxaparin and that was not so. In that regard the Panel considered that the claim was misleading and could not be substantiated. Breaches of Clauses 7.2, 7.3, 7.4 and 7.10 were ruled. The Panel noted that Boehringer Ingelheim had accepted that the claim was in breach of these clauses of the Code. The Panel further considered that the claim did not reflect the available evidence about the safety of Pradaxa. A breach of Clause 7.9 was ruled.

In the Panel's view the advertisement would be read in the context of the licenced doses of Pradaxa and enoxaparin after total knee or hip replacement surgery. The Panel did not accept that because the claim did not state the dose of enoxaparin that it implied that Pradaxa had been shown to be equivalent to any dose of enoxaparin. The Panel did not consider that the claim at issue was misleading because it did not state the dose of enoxaparin. No breach of Clause 7.2 was ruled on that narrow point.

The Panel further noted the allegation that by not referring to the RE-MOBILIZE study, Boehringer Ingelheim had 'cherry-picked' the data. The RE-MOBILIZE study had used a lower dose of enoxaparin ie 30mg/day, than that licensed in the UK for the prevention of VTE following total knee or hip replacement surgery ie 40mg/day. In that regard the Panel did not consider that the claim misled clinicians as to the evidence base to support the claim at issue as alleged. No breach of Clause 7.2 was ruled.

With regard to the activities of sales representatives the Panel noted that the complainant had not made any specific allegations. The front page of the detail aid was visually similar to the advertisement. However, below the depiction of the scale pans was the claim 'Once-daily oral anticoagulation Efficacy and safety *comparable* to enoxaparin' (emphasis added). The claim was referenced to the RE-NOVATE and RE-MODEL studies. Throughout the detail aid Pradaxa and enoxaparin were variously described as being 'comparable' or 'similar'. The detail aid did not describe the two medicines as equivalent. The briefing notes for representatives referred to the comparability of Pradaxa to enoxaparin – not to their equivalence. The Panel did not consider that comparability implied equivalence – comparable only meant that the two products were able to be compared. The Panel did not consider that the material used by the representatives was misleading as alleged. No breach of Clauses 7.2, 7.3, 7.9 and 7.10 was ruled.

The Panel noted its rulings above and did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure.

## APPEAL FROM THE COMPLAINANT

The complainant welcomed the rulings of a breach of the Code but was disappointed that they had not been consistently applied to the representatives' materials which were ruled not to be in breach of the Code. The complainant was concerned that the Panel might have engaged in semantics without regard to the intelligence and common sense of health professionals to whom the claims in question of equivalence/comparability between dabigatran and enoxaparin were aimed.

On one hand the Panel suggested, in previous cases, that non-inferiority studies could not support any direct or implied claims of equivalence, similarity or superiority between two medicines. However, in this case it seemed that the Panel had decided that such studies allowed two medicines to be compared with each other thus allowing claims of comparability ie one medicine was comparable or similar to another. How was this different to assessing equivalence or otherwise?

The complainant questioned the purpose of comparing two medicines if it was not to invite health professionals to consider whether: the two were similar, equivalent, comparable or at least as good as each other; one was worse/inferior than the other; one was better or superior to the other or one was non-inferior to the other. Indeed, this was precisely how the data from non-inferiority studies and other comparative studies was used and considered by regulators, so why not health professionals?

The complainant submitted that the rulings of no breach suggested that sales materials and sales representatives could refer to the actual comparison between dabigatran and enoxaparin described in these non-inferiority studies as long as the materials or representatives somehow avoided inviting a discussion or consideration of the implication of the results to clinicians; this was patently nonsense and not what happened in practice. Did the Panel really suggest that the representatives who used promotional materials which referred to these claims were instructed to present a comparison of the two medicines but leave it to the health professionals to decide for themselves in which of the above four categories the comparison between dabigatran and enoxaparin belonged? This was not what the sales representative briefing instructed regarding the promotion of this claim.

## COMMENTS FROM BOEHRINGER INGELHEIM

Boehringer Ingelheim welcomed the opportunity to comment on the complainant's appeal and strongly endorsed the Panel's rulings of no breach on each of the following points.

**1 Dose of Pradaxa not stated in the advertisement**

Boehringer Ingelheim submitted that the indication for Pradaxa in the prevention of VTE after total hip and knee replacement surgery was clearly stated in the advertisement. The company thus agreed with the Panel's view that the advertisement would be read in the context of the licensed doses of Pradaxa and enoxaparin and so did not imply Pradaxa had

been proven to be equivalent to all doses of enoxaparin. Boehringer Ingelheim endorsed the Panel's ruling of no breach of Clause 7.2.

**2 'Cherry-picking' data**

The RE-MOBILIZE study used the standard regimen of enoxaparin (30mg bd) in the USA which was different from that used within the UK (Europe) (40mg od). In the EU this dosing regimen was not used, nor was it referred to in the SPC and so it was entirely acceptable to not refer to it in UK materials. Boehringer Ingelheim endorsed the Panel's ruling of no breach of Clause 7.2.

**3 The interpretation of 'non-inferiority' studies**

The original complaint referred specifically to a journal advertisement (ref DBG1729b) and also referred to the activity of sales representatives, although did not refer to any specific meeting with representatives nor to any sales materials. Moreover, the complainant did not detail any interactions he had had with the field force that had led to his concerns. This was an important point because the complainant stated that he was a general practitioner. Pradaxa was licensed for the primary prevention of venous thromboembolic events associated with hip and knee replacement surgery ie a specialised orthopaedic area and so Boehringer Ingelheim representatives did not promote Pradaxa to general practitioners. It was unclear how, if at all, this general practitioner could know about the promotion of Pradaxa by Boehringer Ingelheim representatives.

A formal complaint and its subsequent appeal should only be based on fact rather than supposition, otherwise credibility in the PMCPA complaints process could, and would be, questioned. The complainant appeared to have based his appeal on material which Boehringer Ingelheim provided to the PMCPA on request following the complaint. In this regard Boehringer Ingelheim questioned the validity of such an appeal.

The complainant appeared to question the interpretation of non-inferiority studies and the interpretation of their results. Boehringer Ingelheim endorsed the Panel's view that it was acceptable to use 'comparable' or 'similar to' in reference to studies where a medicine had been found to be non-inferior to another. However, there were a number of guidance documents on the subject of demonstrating non-inferiority and its interpretation.

Non-inferiority studies were designed to demonstrate that the difference between two medicines was not clinically relevant. The margin for this difference was set as the delta. In the ICH Guideline on 'Statistical Principles for Clinical Trials', Section 5.2.3 'Roles of Different Analysis Sets' it stated: 'The full analysis set and the per protocol set play different roles in superiority trials (which seek to show the investigational product to be superior), and in equivalence or non-inferiority trials (which seek to show the investigational product to be comparable, see section 3.3.2)'.

In 'Statistical Thinking for Non-statisticians in Drug Regulation' in Chapter 12 'Equivalence and non-inferiority', Section 12.1 'demonstrating similarity' page 174 it was stated: '… in a therapeutic setting we will use a non-inferiority design, where we are looking to establish that our new treatment is 'at least as good as' or 'no worse than' an existing treatment. We will, of course, need to define 'at least as good' or 'no worse than' in an operational sense for this to be unambiguous …'.

In The European Medicines Agency (EMEA) Guideline (EMEA/CPMP/EWP/2158/99) the following was stated '… there are many situations where a non-inferiority trial might be performed as opposed to, or in addition to, a superiority trial over placebo. These include:

- Applications based upon essential similarity in areas where bioequivalence studies are not possible, e.g. modified release products or topical preparations;
- Products with a potential safety advantage over the standard might require an efficacy comparison to the standard to allow a risk-benefit assessment to be made;
- Cases where a direct comparison against the active comparator is needed to help assess risk benefit;
- Cases where no important loss of efficacy compared to the active comparator would be acceptable;
- Disease areas where the use of a placebo arm is not possible and an active control trial is used to demonstrate the efficacy of the test product.'

Non-inferiority studies were inadequate to substantiate claims of 'equivalence' or 'superiority', however, in Boehringer Ingelheim's view, they could substantiate claims of 'similar to' and 'comparable to'. Boehringer Ingelheim considered that 'comparable to' and 'similar to' were synonymous. As acknowledged by the Appeal Board in its consideration of Case AUTH/2270/10/09 'non-inferiority studies showed that even if one product was worse than another it was only worse within clinically unimportant limits'. It must be the case that non-inferiority studies substantiated claims for similarity, as non-inferiority studies frequently provided the clinical data for approval of medicinal products on the basis that they were 'essentially similar' to an existing product.

It also appeared that the complainant might have misunderstood the ruling in Case AUTH/2270/10/09, which he referred to in his complaint. The previous case was about a claim that a product was 'at least as effective as' which, the Panel and Appeal Board considered implied superiority and could not be supported by data from non-inferiority studies alone.

In practice 'comparability' and 'similarity' or 'similar

to' (in relation to non-inferiority studies) were commonly used to describe the interpretation of these results in the academic, promotional and regulatory authority setting.

Boehringer Ingelheim believed that it had demonstrated without doubt that the Panel's rulings of no breach with regard to the points above were correct.

## FINAL COMMENTS FROM THE COMPLAINANT

The complainant stated that he was disappointed that Boehringer Ingelheim appeared to have missed the common sense points he had previously made. Instead the company appeared to question his personal qualification to complain about the promotion of Pradaxa. The complainant noted that he was a Fellow of the Royal College of Surgeons and, as a general practitioner, he had a specialist interest in orthopaedic surgery and worked in the accident and emergency department of his local hospital and as a general practitioner with a special interest in the consultant-led orthopaedics and minor trauma outpatient clinics. Regardless, of the latter, Boehringer Ingelheim appeared to be disconnected from reality if it supposed that general practitioners could only be promoted to by Boehringer Ingelheim's sales representatives. Boehringer Ingelheim's argument was not consistent or credible given that the advertisement for Pradaxa appeared in a non-specialist journal whose UK readership was not restricted to only specialists involved in orthopaedics.

Whilst it might suit Boehringer Ingelheim to skirt around the issue by reference to the EMA and ICH guidelines, what was conveniently obscured was the basic fact that these were relevant to product development and licensing of products but had no direct bearing on product promotion in the UK, the legitimacy of which was judged by reference to the Code.

Similarly, statistician's view, whilst interesting, did not address the fundamental failings of the misleading and unbalanced promotion of Pradaxa compared to enoxaparin by both the UK sales materials and the corporate website. The statistician was not a health professional and did not ultimately bear the responsibility of making an informed prescribing decision which, if based on false and misleading comparative claims, could compromise patient safety.

## APPEAL BOARD RULING

The Appeal Board considered that, it was good practice to include the relevant dosage particulars in claims about medicines. The advertisement included a comparative claim about Pradaxa and enoxaparin without stating the dose of either. The complainant had alleged that this was misleading as it implied that Pradaxa was equivalent to all doses of enoxaparin. The Appeal Board noted, however, that for the primary prevention of VTE following total knee or hip replacement surgery, the only licensed dose of enoxaparin was 40mg daily (some special patient populations might require a lower dose). Given the tightly defined dose of enoxaparin in the general patient population, the Appeal Board did not consider that it was misleading not to have stated the dose in the advertisement. The implication was that the standard licensed dose was being compared, which it was. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.2. The appeal on this point was thus unsuccessful.

The Appeal Board noted that the Panel had incorrectly stated that the RE-MOBILIZE study had used a lower dose of enoxaparin ie 30mg/day, than that licensed in the UK for the prevention of VTE following total knee or hip replacement surgery ie 40mg/day. The RE-MOBILIZE study had used enoxaparin 30mg **twice daily** ie a higher dose than that licensed in the UK. The Appeal Board nonetheless considered that as the RE-MOBILISE study had used a dose of enoxaparin not licensed in the UK, and therefore not relevant to UK prescribers, it was not misleading not to include the study in the evidence base to support the comparative claim at issue. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.2 of the Code. The appeal on this point was thus unsuccessful.

The Appeal Board noted that the complainant had stated in his initial letter to the Authority that he was concerned, *inter alia*, about the promotion of Pradaxa by Boehringer Ingelheim's representatives. The Authority, when it informed the company about the complaint, asked for copies of the Pradaxa detail aid and briefing material. These were subsequently provided. The Appeal Board noted that the detail aid described enoxaparin and Pradaxa as being comparable. The Appeal Board did not consider that this implied equivalence. Given the common understanding of 'comparable' the Appeal Board did not consider that the detail aid was misleading as alleged. The Appeal Board upheld the Panel's rulings of no breach of Clauses 7.2, 7.3, 7.9 and 7.10. The appeal on this point was thus unsuccessful.

The Appeal Board noted its rulings above and upheld the Panel's ruling of no breach of Clause 2 of the Code. The appeal on this point was thus unsuccessful.

**Complaint received** **20 September 2010**

**Case completed** **8 December 2010**