CASE AUTH/2231/5/09

BAYER v BOEHRINGER INGELHEIM

Promotion of Pradaxa

Bayer complained about the promotion of Pradaxa (dabigatran) by Boehringer Ingelheim. The items at issue were a medical information letter and information provided on a Boehringer Ingelheim stand at the British Society for Haematology, April 2009.

Pradaxa was licensed for the primary prevention of venous thromboembolic events in adult patients who had undergone elective total hip or knee replacement surgery. Bayer produced Xarelto (rivaroxaban) which was similarly licensed.

The detailed response from Boehringer Ingelheim is given below.

A letter sent from Boehringer Ingelheim's medical information department to an orthopaedic surgeon noted that the recipient was considering oral antithrombotics in patients undergoing hip or knee replacement surgery and that the letter would update the recipient with information that had become available. Bayer alleged that the letter, which it stated was sent proactively as a mailing rather than in response to an unsolicited request, was promotional and not an objective statement of medical information. High standards had not been maintained.

Bayer noted that the scope of the letter was laid out in the first paragraph as 'the available oral agents for VTE [venous thromboembolism] thromboprophylaxis in patients undergoing hip or knee replacement surgery'. However, under the heading 'Ongoing studies' the letter provided further information about studies in stroke prevention in atrial fibrillation (SPAF) and in VTE treatment. The treatment of SPAF was not connected with VTE prophylaxis in orthopaedic patients.

Bayer alleged that the reference to SPAF and VTE treatment promoted an unlicensed indication and one for which safety was not yet proven in breach of Clause 2.

Bayer alleged that the promotional (and off-label) references to SPAF and other indications constituted a breach of an inter-company undertaking.

Bayer was very concerned about a claim in the letter about the requirement for pre-operation liver function tests (LFTs) relating to alanine transaminase (ALT) for patients on dabigatran: 'This one-off [ALT] measurement … should not typically require the taking of additional blood over and above the usual routine. Importantly, any subsequent LFT testing or LFT monitoring is not required for Pradaxa'. Bayer alleged that the reference to 'usual routine' was misleading because it implied that this blood test was part of the routine pre-operative work-up. However, LFTs were not part of the routine pre-operative work-up as defined by the National Institute for Health and Clinical Excellence (NICE). The claim was misleading and could not be substantiated. Bayer was also concerned that the unqualified claim 'any subsequent LFT testing or LFT monitoring is not required' misled. Changes in liver function parameters were listed as undesirable effects in the Pradaxa SPC, and so Boehringer Ingelheim could not substantiate the claim that measurement of LFTs was not required.

Bayer also alleged that the section entitled 'Balance between efficacy and bleeding' and the statement 'There is some concern as to whether the superior efficacy achieved by Xarelto (rivaroxaban) is at the cost of increased bleeding risk' encapsulated the tone of this entire section of the letter and disparaged rivaroxaban. Bayer alleged that the letter did not represent the balance of evidence with regard to safety results for rivaroxaban.

There was no mention of the positive efficacy benefits and overall positive net clinical benefit demonstrated in each of four rivaroxaban studies (RECORD 1, 2, 3 and 4) and in the pooled analysis of these studies. Bayer's primary efficacy endpoint was reached (and in fact superiority demonstrated) for all individual studies and for the pooled analysis at all time points considered. This fact, and the risk-benefit balance it entailed, was not alluded to in the letter. This omission was disparaging, unbalanced and did not represent the data as a whole. High standards had not been maintained.

Bayer noted that the letter referred to negative information including the Bayer-sponsored RECORD 4 study, but failed to mention the Boehringer Ingelheim equivalent study (REMOBILIZE) which failed to reach its pre-specified primary endpoint. This was a further failure to be balanced and fair.

Bayer alleged that the statement in the letter that the concomitant use of epidural catheters 'needs careful consideration' conflicted with the wording in the summary of product characteristics (SPC) and was likely to confuse.

The Panel noted that both parties agreed that the letter at issue had been sent by Boehringer Ingelheim's medical information department to a health professional. Boehringer Ingelheim

submitted that the letter could take the benefit of the exemption to the definition of promotion set out in the Code; it was a non-promotional response to an unsolicited enquiry from a health professional. The Panel noted that to take the benefit of the exemption the response to an unsolicited enquiry must not be promotional, go beyond the ambit of the original enquiry or be misleading; the response must be accurate. The recipient of the letter at issue wished to remain anonymous and so Boehringer Ingelheim was unable to identify the original enquiry. Boehringer Ingelheim submitted that the request for information would have arisen during the course of a representative visit. Bayer, however, alleged that the letter at issue was sent proactively to the recipient and potentially to many other health professionals. The Panel noted that the burden fell on Bayer to establish its case on the balance of probabilities. Bayer had submitted no evidence to support its submission that the letter at issue was a circular mailing. The Panel considered that the position was complicated in that the identity of the recipient had not been revealed to Boehringer Ingelheim and its author had left the company. The Panel noted that Boehringer Ingelheim acknowledged that it needed to improve the level of detail it recorded for each request; the letter at issue could have been sent to any one of thirteen requests via representatives for information on the comparisons of bleeding and other data between rivaroxaban and dabigatran. In the Panel's view particular care needed to be taken when requests for information resulted from a meeting with a representative. Companies wishing to take the benefit of the exemption to the definition of promotion had to be able to demonstrate that the request was unsolicited.

The Panel noted Boehringer Ingelheim's submission about the scope of the original enquiry. The letter at issue began 'I understand that you are carefully considering the available oral agents for VTE thromboprophylaxis in patients undergoing hip or knee replacement surgery. I wish to take this opportunity to update you with the information that has become available'. The Panel considered that it was not unreasonable to assume that this paragraph reflected the original enquiry.

Pradaxa was licensed for the primary prevention of venous thromboembolic events in adult patients who had undergone elective total hip or total knee replacement surgery. The penultimate paragraph of the letter headed 'Ongoing studies' referred to a study on the use of Pradaxa in SPAF. Pradaxa was not licensed for SPAF. The Panel noted all its comments above about the status of the letter and whether it could take the benefit of the exemption to the definition of promotion. It was unclear whether the enquiry was solicited or unsolicited. The Panel considered that, on the balance of probabilities, by referring to SPAF, the letter might well have gone beyond the scope of the original enquiry outlined at the beginning of the letter which meant that it could not take the benefit of the exemption. The Panel considered that the letter promoted Pradaxa for an unlicensed indication and was inconsistent with the particulars listed in its SPC. A breach of the Code was ruled.

The Panel did not consider that the reference to the unlicensed indication represented a breach of Clause 2.

The Panel noted that the introductory section of the letter referred to the misconception that LFT monitoring was necessary with Pradaxa and stated that the recommendation for Pradaxa was that a one-off baseline ALT measurement be made during the pre-operative assessment. The letter also stated that this one-off measurement to assess the patient should not typically require the taking of additional blood over and above usual routine and that 'Importantly any subsequent LFT testing or LFT monitoring is not required for Pradaxa'. The Panel noted Boehringer Ingelheim's submission that patients routinely gave a blood sample pre-op and that if LFT testing was not normally included it could be added without additional blood being taken. The Panel did not consider that the section at issue misleadingly implied that LFTs were part of the routine pre-operative work defined by NICE as alleged. NICE was not mentioned at all in the letter. No breaches of the Code were ruled. Neither did the Panel consider that the section was misleading as to Pradaxa's safety profile as alleged or incapable of substantiation in this regard. The section discussed the one-off baseline ALT assessment. Adverse events subsequent to administration of Pradaxa was a separate matter. Hepatobiliary disorders occurred in less than 1% of patients. No breaches of the Code were ruled.

The Panel noted that the section entitled 'Balance between efficacy and bleeding' explained that for all new oral anticoagulants there was a need for a balance between efficacy and bleeding risk. It continued 'There is some concern as to whether the superior efficacy achieved by Xarelto (rivaroxaban) was at the cost of increased bleeding risk'. This was followed by a reference to an enclosed summary of the rivaroxaban pooled RECORD study data which included pooled bleed data which showed significance. Bayer stated that it had not been provided with a copy of the summary following a request to Boehringer Ingelheim.

The Panel noted that the review by Frostick discussed the RECORD 1, 2 and 3 studies wherein rivaroxaban was compared with enoxaparin. It was noted that there was no head-to-head comparison of dabigatran and rivaroxaban; Pradaxa and rivaroxaban had each been compared to enoxaparin in separate non-inferiority studies wherein the safety profiles of each showed no statistically significant between group difference. The author concluded that the data seemed to indicate that rivaroxaban might be associated with a greater risk of bleeding which could be a major disadvantage.

The Panel also noted that NICE guidance 170 commented on the RECORD data noting that rivaroxaban at 10mg daily might be more efficacious than enoxaparin in preventing VTE but this was accompanied by a small increased risk of major bleeding. The Committee agreed that on balance rivaroxaban and dabigatran had broadly similar efficacy profiles and noted the need to balance prevention of VTE with possible adverse effects particularly the incidence of major bleeds.

Attached to the letter at issue was, , a pooled analysis of the four RECORD studies based on a presentation by Turpie (2008) and a bleeding definition paper. The RECORD studies each investigated rivaroxaban for the prevention of venous thromboembolism in patients undergoing major orthopaedic surgery vs enoxaparin. The pooled analysis concluded that for the total treatment duration significantly more bleeding was seen with rivaroxaban than enoxaparin for the combined category major bleeding plus clinically relevant non-major bleeding. The published abstract Turpie (2008) concluded, *inter alia*, that rivaroxaban was not associated with a statistically significant increase in the risk of major bleeding. The Panel noted Bayer's submission that only one of the Bayer composite endpoints for bleeding reached significance and only at a single time point that included patients receiving placebo vs rivaroxaban in RECORD 2. Boehringer Ingelheim data on file analysed the bleeding definitions and bleeding rates in the REVOLUTION study programme (Pradaxa) compared to RECORD and noted that a decision was made to change the bleeding definition for the RECORD phase III programme which could be directly responsible for the low overall events rates within the major bleeding category reported in the clinical trials.

The Panel noted that the claim 'There is some concern as to whether the superior efficacy achieved by Xarelto was at the cost of increased bleeding risk' in the letter would be read as a direct comparison with Pradaxa and this was not so. The RECORD studies compared rivaroxaban with enoxaparin. There was only indirect comparative data for Pradaxa and Xarelto. The letter had not provided sufficient detail about the comparisons and was thus disparaging. A breach of the Code was ruled.

The Panel considered that the letter by stating without further explanation that the pooled bleed data 'shows significance' over simplified the position and gave a misleading impression of the totality of the bleed data. A breach of the Code was ruled. On balance, the Panel did not consider that the reference to significance was disparaging as alleged. No breach of the Code was ruled.

The Panel did not consider that the failure to discuss the efficacy of rivaroxaban as demonstrated in the RECORD studies was misleading or disparaging as alleged. The letter made it clear that rivaroxaban achieved superior efficacy. No breaches of the Code were ruled.

The Panel noted Boehringer Ingelheim's submission that medical information was rarely asked about the relative efficacy of rivaroxaban and Pradaxa. The letter referred to the balance between efficacy and bleeding it did not detail the products' relative efficacy and thus the Panel did not consider that the failure to refer to the REMOBILIZE study was misleading as alleged. No breach of the Code was ruled.

The Panel noted that the letter stated that the insertion/removal of epidural catheters in the presence of an anticoagulant needed careful consideration and referred to an enclosed information sheet. The Panel noted the Pradaxa SPC stated that Pradaxa was not recommended for use in patients undergoing anaesthesia with post-operative indwelling epidural catheters. The Panel noted that whilst this cautionary wording was reflected in the information which accompanied the letter, the letter had to be able to stand alone as regards the requirements of the Code. The Panel considered that given the wording of the SPC the letter was misleading about the concomitant use of catheters and the administration of Pradaxa and inconsistent with the particulars listed in its SPC. Breaches of the Code were ruled.

The Panel noted that its rulings of breaches of the Code outlined above demonstrated that the letter was, in part, inaccurate and misleading were further reasons why the letter could not take the benefit of the exemption to the definition of promotion.

The Panel noted that Bayer had also alleged a breach of the Code as the letter was promotional throughout and not an objective statement of medical information. The Panel considered that health professionals and others should be able to rely upon medical information departments as a source of objective information about products. The Panel noted its rulings of breaches of the Code and the Panel considered that the letter as a whole failed to maintain high standards. A breach of the Code was ruled.

Bayer alleged that Boehringer Ingelheim's stand at a meeting of the British Society for Haematology, April 2009 promoted ongoing clinical trials of dabigatran in unlicensed indications, including life size trial logos in brand colours. Bayer alleged a breach of the Code because it was not in accordance with the terms of the Pradaxa marketing authorization. The safety and efficacy data for these trials were not yet available.

Bayer alleged that this provision of information about clinical trials was promotional in nature in breach of the Code including Clause 2.

The Panel noted that the exhibition stand presented information about the REVOLUTION clinical trial programme: acute VTE treatment;

secondary VTE prevention; SPAF and secondary prevention of cardiac events in patients with acute coronary syndrome. The Panel noted the submission that the stand had been set up to meet an anticipated demand for information beyond VTE prevention. The Panel disagreed with the submission that only interested physicians would visit and seek information. The stand panels included a section listing features of dabigatran, a reference to what appeared to be a Boehringer Ingelheim meeting 'A Question of Anticoagulation' and stated that medical information was available on request. In the Panel's view such a statement would solicit requests. Boehringer Ingelheim submitted that the logos used on the stand were for the clinical studies mentioned and no product branding was included. The stand was manned by medical affairs and medical information staff. Boehringer Ingelheim had provided the briefing document to the sales team regarding UK congresses which stated that the REVOLUTION stand was used in addition to the normal branded stand pre-launch.

The Panel was concerned about the stand; its presence demonstrated a poor understanding of the requirements of the Code. Placing documents on an exhibition stand amounted to an invitation to take them. The Panel considered that the exhibition stand at issue solicited enquiries about dabigatran and the REVOLUTION clinical trial programme. The Panel noted that Pradaxa was licensed for the primary prevention of VTE following elective total hip or total knee replacement surgery. The Panel considered that the exhibition stand promoted Pradaxa for unlicensed indications and this was inconsistent with the SPC. A breach of the Code was ruled. As Pradaxa was promoted prescribing information needed to be provided or made available at the stand. A breach of the Code was ruled. The Panel did not consider that the promotional activity was disguised as alleged. No breach of the Code was ruled. The Panel did not consider that the stand at issue represented a failure to disclose details of clinical trials as required by the Code. The supplementary information to that clause reminded companies that such information must not constitute promotion. That aspect was covered by the Panel's rulings outlined above. No breach of the Code was ruled.

Although seriously concerned about the stand, on balance the Panel did not consider that a ruling of a breach of Clause 2 of the Code was warranted. This was reserved for use as a sign of particular censure.

Bayer plc complained about the promotion of Pradaxa (dabigatran) by Boehringer Ingelheim Limited. The items at issue were a medical information letter and information provided at a Boehringer Ingelheim stand at the British Society for Haematology, 49th Annual Scientific Meeting, 27-29 April 2009.

Pradaxa was licensed for the primary prevention of venous thromboembolic events in adult patients who had undergone elective total hip replacement surgery or total knee replacement surgery. Bayer produced Xarelto (rivaroxaban) which was similarly licensed.

* * * * *

The Panel noted that although Bayer had not always cited specific sub-clauses of the Code when alleging breaches of Clauses 3, 7, 8 and 9, it had provided sufficient information such that its allegations clearly related to specific sub-clauses. Nonetheless the Panel noted that complainant companies should always cite the specific sub-clauses to be considered.

1 Medical information letter

A letter sent from the medical information department, Boehringer Ingelheim, to a health professional noted that the recipient was considering oral antithrombotics in patients undergoing hip or knee replacement surgery and that the letter would update the recipient with information that had become available. The health professional to whom the letter was addressed had proactively given an anonymised copy of it to Bayer.

COMPLAINT

Bayer alleged that this letter was sent proactively to an orthopaedic surgeon (and hence potentially to many other health professionals as a circular mailing) rather than in response to a genuine unsolicited request. This was a breach of Clause 1.2 firstly because the first paragraph stated 'I wish to take this opportunity to update you …' and 'information that has become available' rather than 'Further to your request for information …' which would normally be the correct procedure for an unsolicited request for information. Secondly, the recipient felt that anonymity would be ensured by removing his name and the date from the top of the letter; he did not view this as an individual personalised letter sent specifically to him, but rather as a widely circulated piece.

Bayer alleged that the letter was promotional in tone throughout, and was not an objective statement of medical information. As well as the breach of Clause 1, this constituted a failure to maintain high standards in breach of Clause 9. Use of the brand name, Pradaxa rather than the generic name dabigatran, which was customary in non-promotional communications, particularly in relation to prescribing indications in respect of which no marketing authorization had been granted. Further, promotional statements and disparaging comments were made about competitor products – especially rivaroxaban – throughout the letter.

Bayer alleged that the scope of the letter was wider than would be the case for a response directly and solely related to the particular enquiry as stipulated

in Clause 1.2. The scope of the letter (whether genuinely unsolicited or otherwise) was laid out in the first paragraph as 'the available oral agents for VTE [venous thromboembolism] thromboprophylaxis in patients undergoing hip or knee replacement surgery'. In contrast to this, under the heading 'Ongoing studies' the letter provided further information about Boehringer Ingelheim studies in stroke prevention in atrial fibrillation (SPAF) and in VTE treatment. The treatment of SPAF was not connected with VTE prophylaxis in orthopaedic patients.

Bayer alleged that the inclusion of SPAF and VTE treatment constituted a breach of Clause 3; the comparative statement about dabigatran's SPAF timelines as being 'ahead in terms of timescale ... of all new anticoagulants' gave the letter an overtly promotional tone. Boehringer Ingelheim did not have a marketing authorization for dabigatran in these indications, and in addition, the safety and efficacy results of these studies were not yet known. Bayer alleged that the letter therefore promoted an unlicensed indication and one for which safety was not yet proven in breach of Clause 2. Use of the brand name Pradaxa rather than dabigatran introduced a promotional tone.

Bayer alleged that following Boehringer Ingelheim's satellite symposium at the meeting in 2008 and subsequent inter-company dialogue, Boehringer Ingelheim gave an assurance that it would be more sensitive about the perception of off-label promotion of dabigatran in SPAF in future. However the promotional (and off-label) references to SPAF and other indications constituted a breach of the undertaking given by Boehringer Ingelheim, in breach of Clause 25, and reopened the issue of the satellite symposium invitation according to the inter-company agreement.

Bayer was very concerned about the following sentences in the medical information letter relating to the requirement for pre-operation liver function tests (LFTs) relating to alanine transaminase (ALT) for patients on dabigatran: 'This one-off [ALT] measurement … should not typically require the taking of additional blood over and above the usual routine. Importantly, any subsequent LFT testing or LFT monitoring is not required for Pradaxa'. Bayer alleged that the section about 'usual routine' was misleading because it implied that this blood test was part of the routine pre-operative work-up. However, LFTs were not part of the routine pre-operative work-up as defined by the National Institute for health and Clinical Excellence (NICE). The claim was misleading and could not be substantiated in breach of Clause 7.

Bayer was particularly concerned that the unqualified claim 'any subsequent LFT testing or LFT monitoring is not required' was misleading as to the safety profile of dabigatran. Derangements of liver function parameters were listed as undesirable effects in the Pradaxa SPC, and therefore Boehringer Ingelheim could not substantiate the claim that measurement of LFTs was not required in breach of Clause 7.

Bayer also alleged that in the section entitled 'Balance between efficacy and bleeding', the statement 'There is some concern as to whether the superior efficacy achieved by Xarelto (rivaroxaban) is at the cost of increased bleeding risk' encapsulated the tone of this entire section of the letter and disparaged rivaroxaban, in breach of Clause 8.

Bayer alleged that the letter did not represent the RECORD safety results for rivaroxaban as a whole – only of the single significant adverse safety composite result. Bayer noted that only one of the composite endpoints for bleeding reached significance, and only at a single time point that included patients receiving placebo vs rivaroxaban in RECORD 2. None of the other composite or single safety endpoints reached statistical significance at any time point considered. Despite this, however, the wording in the medical information letter 'this includes pooled data (which shows significance) …' implied that overall the pooled data demonstrated a significant increase in bleeding rates. This was disparaging and unbalanced in breach of Clauses 1, 7 and 8.

There was no mention of the positive efficacy benefits and overall positive net clinical benefit demonstrated in each of the rivaroxaban studies (RECORD 1, 2, 3 and 4) and in the pooled analysis of these studies. Bayer's primary efficacy endpoint was reached (and in fact superiority demonstrated) for all individual studies and for the pooled analysis at all time points considered. This fact, and the risk-benefit balance it entailed, was not alluded to in the letter. This was disparaging in breach of Clause 8, unbalanced and did not represent the data as a whole (Clause 7). This was inappropriate wording for a medical information letter which would be expected to be objective (Clause 1). This was a clear failure to maintain high standards (Clause 9).

Bayer noted that the letter referred to negative information including the Bayer-sponsored RECORD 4 study, but failed to mention the Boehringer Ingelheim equivalent study (REMOBILIZE) which failed to reach its pre-specified primary endpoint. This was a further failure to be balanced and fair as required by Clauses 1 and 7.

The letter referred to an 'enclosed information sheet'. In view of its concerns expressed above Bayer asked for a copy of this information sheet as it suspected that it might contain similarly biased reporting. However this request was not acceded to by Boehringer Ingelheim.

The letter failed to make it explicit that the concomitant use of epidural catheters was 'not recommended' in the Pradaxa SPC. On the contrary, the statement in the letter that this 'needs careful consideration' conflicted with the wording in the SPC and was likely to confuse. The reference to

'careful consideration' was outside Pradaxa's label (breach of Clause 3). Bayer alleged that referring the reader to a separate enclosure without describing the content of the enclosure in the main text was inadequate to get around this, in the same way that Clause 7 stated that claims should not be qualified by the use of 'footnotes and the like'. The use of the separate enclosure was a breach of Clause 7.

In inter-company dialogue, Boehringer Ingelheim stated that it was difficult to investigate Bayer's complaint without knowing who the customer was. Boehringer Ingelheim did not refer to any discussion of the matter with the medical information officer who wrote the letter or to any search of the medical information database to find the original specific enquiry.

RESPONSE

Boehringer Ingelheim explained that medical information sent the letter in response to an unsolicited request for information from a health professional. The request would have been forwarded to medical information by a sales representative using the company's information system. As was normal practice the response consisted of specific pre-prepared sections and/or attachments that covered the matters of the request. Subsequent investigation of the details of the requesting physician, the specific sales representative and the details of the request had been hampered by the fact that the medical information officer in question had left Boehringer Ingelheim.

Boehringer Ingelheim submitted that although the date was obscured the letter was sent in 2009. The company's information system showed that between 1 January 2009 and 18 February 2009 the medical information department sent out thirteen responses with information on the comparison of bleeding and other data between rivaroxaban and dabigatran.

Boehringer Ingelheim submitted that this was the first time that it had needed to analyse the system to identify a specific request in this way and by undertaking this process it recognised a need for further improvement in the level of detail recorded for each request. This was being implemented for future requests. Boehringer Ingelheim had re-enforced to the field force to clearly outline how and what to request through medical information. Boehringer Ingelheim had also re-emphasised to its medical information team the importance of the most optimal response to customer enquiries. Boehringer Ingelheim informed Bayer of this (7 May 2009).

Unfortunately, without further information, Boehringer Ingelheim had not been able to identify the specific request that this letter related to.

Boehringer Ingelheim submitted that the request for comparative information on rivaroxaban and dabigatran in this letter would have arisen during the course of a representative visit to a health professional. This was, not surprisingly, a common request as there were just two relatively new oral anticoagulants for VTE prophylaxis associated with knee and hip replacement surgery and decisions on which to include in potential formularies or to prescribe were influenced by differences in recommendations or performance in specific clinical situations. Boehringer Ingelheim submitted that some clinicians considered that a formulary application was unlikely to be successful for VTE prophylaxis in isolation and so they requested further information on the likely timings of a wider range of indications. This was why information on ongoing off-label studies was included. The representative forwarded such requests to medical information and the response was sent directly to the health professional.

Boehringer Ingelheim denied that this letter was sent proactively to a number of health professionals. For the reasons outlined above, the recipient could not be identified but as a policy medical information responses were specific and sent only upon receipt of a request.

Boehringer Ingelheim disagreed that medical information letters must begin with 'Further to your request for information …' or the like. Indeed in this case the breadth of requested information would make such an introduction quite cumbersome as it would require all the topics covered to be listed. However, to avoid the possible motive for a future medical information letter being similarly misunderstood, Boehringer Ingelheim had instructed the medical information team to refer, within the introductory paragraph, to the sales representative visit from which the request had arisen and to ensure there was a clear reference to specific requests for each of the subjects covered in the response.

Boehringer Ingelheim denied that the letter was promotional in tone throughout and was not objective. 'Pradaxa', which appeared more than once in the body of the letter and also in the information sheet related to epidural anaesthesia, was not used throughout; dabigatran was used on a number of occasions. Including the brand name more than once in the letter was an oversight which had been corrected as referred to in inter-company dialogue. However, while minimising use of the brand name was good practice, Boehringer Ingelheim did not consider its use was necessarily a breach of the Code. The format of the communication was clearly a letter and it did not appear promotional.

Boehringer Ingelheim disagreed with Bayer's submission that the scope of the letter was wider than would be the case for a response directly and solely to a particular enquiry. In considering points of difference between dabigatran and rivaroxaban, the topics included in this letter were all relevant and ones upon which Boehringer Ingelheim was

frequently asked for information either individually or in combination. As described above, the progress of ongoing studies in indications which health professionals seemed to perceive as more important than VTE prophylaxis in knee and hip replacement surgery was an area of considerable interest and therefore a frequent subject of request. Boehringer Ingelheim was unable to comment upon whether the recipient of this letter was an orthopaedic consultant. The information presented on ongoing studies was factually correct and the content was entirely appropriate in a medical information response to an unsolicited request for information. Boehringer Ingelheim denied that this was promotional and did not agree that this was in breach of Clause 3 of the Code as alleged. Further, in relation to the provision of information on ongoing studies Bayer alleged a breach of undertaking with regard to previous inter-company dialogue in a separate matter. Boehringer Ingelheim understood however that Clause 25 related to undertakings in respect of rulings under the Code which would not apply in this case.

Boehringer Ingelheim disagreed with Bayer's allegation that the information about the requirement for LFTs with dabigatran was misleading. The statement 'This one off [ALT] measurement …should not typically require the taking of additional blood over and above the usual routine. Importantly subsequent LFT testing or LFT monitoring is not required for Pradaxa' was accurate and reflected both the Pradaxa SPC and clinical practice. The section about usual routine was accurate and was not misleading as routine pre-operative work-up normally included venepuncture for blood chemistry (and haematology). Where LFT was not normally included in the routine blood chemistry analysis it could be added (usually by box ticking on the same request form) and no additional blood would be required for this analysis. It was also possible that where routine pre-operative screening without LFT had been completed the laboratory might be asked over the following few days to perform LFTs on the retained sample. That NICE did not include LFT in routine pre-operative work-up was irrelevant as Boehringer Ingelheim did not indicate that this was routine. Boehringer Ingelheim indicated only that LFT could be undertaken without need for additional blood. The further statement that any subsequent LFT testing or monitoring was not required was accurate and consistent with the SPC. It was correct that derangements of LFTs were included among the adverse reactions reported with dabigatran but this was an entirely separate matter from any requirement for routine monitoring of LFT subsequent to the pre-operative sample. Request for clarification of the requirements for LFT testing with dabigatran was not infrequent from health professionals who had received misinformation on the requirements for LFT monitoring with dabigatran.

Bayer had complained that the statement 'There is some concern as to whether the increased efficacy achieved by Xarelto is at the cost of increased bleeding' disparaged rivaroxaban. Boehringer Ingelheim submitted that this was an accurate statement that reflected both clinician views (Frostick 2009);

> 'The safety data, however, seem to indicate that rivaroxaban may be associated with a greater risk of bleeding (as shown in the pooled data analysis). As surgical site bleeding is the major concern for orthopaedic surgeons, increased bleeding risk with rivaroxaban could be a major disadvantage for the drug', and

The NICE technology appraisal guidance 170:

> '4.5 The Committee discussed the results of the RECORD studies and concluded that rivaroxaban was at least as effective as enoxaparin in preventing VTE. The Committee considered adverse events such as bleeding, noting that the relative risk of major bleeding numerically favoured enoxaparin. The Committee noted that the chosen dose of rivaroxaban appeared to increase efficacy in prevention of VTE after surgery, with a small increase in risk of major bleeding when compared with enoxaparin. It concluded that rivaroxaban at its licensed dosage of 10 mg daily might be more efficacious than enoxaparin in preventing VTE but this was accompanied by a small increased risk of major bleeding. The Committee was persuaded by testimony from the clinical specialists that there was a 'brand off' to be made between increasing anticoagulant efficacy and the risk of adverse effects, including major bleeding.
>
> 4.6 The Committee considered evidence on the clinical effectiveness of rivaroxaban compared indirectly with dabigatran that showed that rivaroxaban significantly reduced the relative risk of the major primary endpoints. However, the Committee noted that in this analysis the relative risk of major bleeding favoured dabigatran although this difference was not statistically significant. It agreed that on balance, rivaroxaban and dabigatran had broadly similar efficacy profiles, and noted the need to balance prevention of VTE with possible adverse effects, particularly the incidence of major bleeding events.'

In addition to this, the FDA Advisory Committee Briefing Document for New Drug Applications 22-406 addressed the concerns of bleeding events for patients undergoing total hip or knee replacement surgery receiving treatment of rivaroxaban compared with enoxaparin.

Bayer had expressed a number of concerns related to the two paragraphs headed 'Balance between efficacy and bleeding'. It was well established that

with anticoagulants increased effect was associated with an increased risk of bleeding although clearly this needed to be demonstrated for individual products.

It was important to understand the context of the requests for information and therefore also the responses. Rivaroxaban had demonstrated superior efficacy to enoxaparin in an extensive phase III clinical trial programme whereas dabigatran had shown non-inferiority to enoxaparin (in a phase III programme designed with this objective). The efficacy of rivaroxaban was generally well accepted by clinicians (and Boehringer Ingelheim) and medical information was rarely asked about relative efficacy.

Understanding of the risks of bleeds with rivaroxaban relative to dabigatran was very difficult to assess objectively based upon the clinical study data. In the rivaroxaban clinical studies the definitions of bleeding events were different from the traditional definitions used in the studies of dabigatran and other products in this area. Related to this the rate of bleeding events for both active and control were much lower in the rivaroxaban studies than in studies of dabigatran and other earlier products eg enoxaparin and fondaparinux. Understanding differences in the definitions of bleeding events between studies was clearly critical to interpretation of results. Many clinicians did not know of these differences but when they did they requested specific information.

Boehringer Ingelheim submitted that this letter provided such information. Copies of the rivaroxaban and dabigatran publications and published information from the pooled analysis conducted by Bayer were provided.

Boehringer Ingelheim submitted that in the individual rivaroxaban studies there were no significant differences in bleeding events between rivaroxaban and enoxaparin although numerically the incidence of bleeding was greater with rivaroxaban. The low overall incidence of major bleeding events, at least in part related to the restrictive definition of an event, would statistically reduce the likelihood that a numerical difference would achieve statistical significance. Bayer undertook a pooled analysis of efficacy and safety endpoints and it was these data that Boehringer Ingelheim had summarised in its response.

Boehringer Ingelheim submitted that the statements in the letter in conjunction with the information sheets, which provided the details reflected an accurate and balanced review relevant to a request for clarification of differences in bleeding definitions used in the dabigatran and rivaroxaban study programmes and an objective view of the bleeding risk with rivaroxaban (relative to enoxaparin).

Boehringer Ingelheim submitted that with regard to the information on 'concomitant use of epidural catheters' it was important to consider the context within which the information was provided, specifically a request for comparative information on rivaroxaban and dabigatran and their use with epidural catheters. Boehringer Ingelheim submitted that the paragraph in the body of the letter was clear and accurate and specifically referred the reader to the enclosed information sheet. It made only a general statement without any specific statement about the use of either product in relation to epidural catheters. Boehringer Ingelheim submitted this was clear, unambiguous and would not confuse. The information sheet enclosed with the letter provided the detailed information and was similarly accurate, unambiguous and reflected the SPCs.

Copies of the information sheets referred to in the medical information letter were provided.

PANEL RULING

The Panel noted that both parties agreed that the letter at issue had been sent by Boehringer Ingelheim's medical information department to a health professional. Boehringer Ingelheim submitted that the letter could take the benefit of the exemption to the definition of promotion set out in Clause 1.2; it was a non-promotional response to an unsolicited enquiry from a health professional. The Panel noted that to take the benefit of the exemption the response to an unsolicited enquiry must not be promotional, go beyond the ambit of the original enquiry or be misleading; the response must be accurate. The recipient of the letter at issue wished to remain anonymous and so Boehringer Ingelheim was unable to identify the original enquiry. Boehringer Ingelheim submitted that the request for information would have arisen during the course of a representative visit. Bayer, however, alleged that the letter at issue was sent proactively to the health professional, an orthopaedic surgeon, and potentially to many other health professionals. The Panel noted that the burden fell on Bayer to establish its case on the balance of probabilities. The Panel noted that Bayer had submitted no evidence to support its submission that the letter at issue was a circular mailing. The Panel considered that the position was complicated in that Boehringer Ingelheim had not been provided with the name of the recipient of the letter and its author had left the company. The Panel noted that Boehringer Ingelheim acknowledged that it needed to improve the level of detail it recorded for each request. Thirteen responses, sent between 1 January and 18 February 2009, to requests via representatives for information on the comparisons of bleeding and other data between rivaroxaban and dabigatran had been identified by Boehringer Ingelheim. In the Panel's view particular care needed to be taken when requests for information resulted from a meeting with a representative. Companies wishing to take the benefit of the exemption to the definition of promotion had to be able to demonstrate that the request was unsolicited.

The Panel noted that Bayer had commented on the use of the brand name in the letter. The use of the brand name did not necessarily mean that the letter was promotional and thus could not take the benefit of the exemption to Clause 1.2. Equally the use of the generic name did not necessarily mean the letter was non-promotional.

The Panel noted that Bayer had alleged a breach of Clause 1.2. The Panel noted that Clause 1.2 was an explanatory clause which set out, *inter alia*, the definition of promotion, examples of promotional activity and material and exemptions to the definition of promotion. It was not a clause which was capable of infringement. The Panel thus made no ruling on all of the alleged breaches of Clause 1.2 at point 1.

The Panel noted Boehringer Ingelheim's submission about the scope of the original enquiry. The letter at issue began 'I understand that you are carefully considering the available oral agents for VTE thromboprophylaxis in patients undergoing hip or knee replacement surgery. I wish to take this opportunity to update you with the information that has become available'. The Panel considered that it was not unreasonable to assume that this paragraph reflected the original enquiry.

The Panel noted that Pradaxa was licensed for the primary prevention of venous thromboembolic events in adult patients who had undergone elective total hip replacement surgery or total knee replacement surgery. The penultimate paragraph of the letter at issue headed 'Ongoing studies' discussed the relatively early publication of the Pradaxa study in SPAF (stroke prevention in arterial fibrillation) compared to SPAF studies of all other new anticoagulants. This was the first mention of SPAF in the letter. Pradaxa was not licensed for SPAF. The Panel noted all its comments above about the status of the letter and whether it could take the benefit of the exemption to the definition of promotion set out in Clause 1.2 of the Code. It was unclear whether the enquiry was solicited or unsolicited. The Panel considered that, on the balance of probabilities, by including the reference to SPAF, the letter might well have gone beyond the scope of the original enquiry outlined at the beginning of the letter which meant that it could not take the benefit of the exemption in Clause 1.2 to the definition of promotion. The Panel considered that the letter promoted Pradaxa for an unlicensed indication and was inconsistent with the particulars listed in its summary of product characteristics (SPC). A breach of Clause 3.2 was ruled.

The Panel did not consider that the reference to the unlicensed indication represented a breach of Clause 2 as alleged which was reserved as a sign of particular censure. No breach of Clause 2 was ruled.

The Panel noted that Bayer had alleged a breach of undertaking in relation to Boehringer Ingelheim's failure to comply with an inter-company agreement about references to Pradaxa and SPAF. The Panel noted that Clause 25 applied solely to undertakings given to the Authority in relation to rulings made under the Code. It did not apply to agreements reached during inter-company dialogue. No breach of Clause 25 was ruled.

The Panel noted that the introductory section of the letter referred to the misconception that LFT monitoring was necessary with Pradaxa and stated that the recommendation for Pradaxa was that a one-off baseline ALT measurement be made during the pre-operative assessment. The letter also stated that this one-off measurement to assess the patient should not typically require the taking of additional blood over and above usual routine and that 'Importantly any subsequent LFT testing or LFT monitoring is not required for Pradaxa'. The Panel noted Boehringer Ingelheim's submission that routine pre-operative work normally included venepuncture for blood chemistry and haematology; if LFT testing was not normally included it could be added without the patient giving additional blood. The Panel did not consider that the section at issue gave the misleading impression that measurement of LFTs was part of the routine pre-operative work defined by NICE as alleged. NICE was not mentioned at all in the letter. No breach of Clauses 7.2 and 7.4 was ruled. Neither did the Panel consider that the section was misleading as to Pradaxa's safety profile as alleged or incapable of substantiation in this regard. The section discussed the one-off baseline ALT assessment. Adverse events subsequent to administration of Pradaxa was a separate matter. Hepatobiliary disorders occurred in less than 1% of patients. No breach of Clauses 7.2, 7.4 and 7.9 was ruled.

The Panel noted that the section entitled 'Balance between efficacy and bleeding' explained that for all new oral anticoagulants there was a need for a balance between efficacy and bleeding risk. It continued 'There is some concern as to whether the superior efficacy achieved by Xarelto (rivaroxaban) was at the cost of increased bleeding risk'. This was followed by a reference to an enclosed summary of the rivaroxaban pooled RECORD study data which included pooled bleed data which showed significance. Bayer stated that it had not been provided with a copy of the summary following a request to Boehringer Ingelheim.

The Panel noted that the review by Frostick discussed the RECORD 1, 2 and 3 studies wherein rivaroxaban was compared with enoxaparin. It was noted that there was no head-to-head comparison of dabigatran and rivaroxaban; Pradaxa and rivaroxaban had each been compared to enoxaparin in separate non-inferiority studies wherein the safety profiles of each showed no statistically significant between group difference. The author concluded that the safety data seemed to indicate that rivaroxaban might be associated with a greater risk of bleeding (as shown in the pooled data analysis of RECORD 1, 2, 3 and 4) and that the increased bleeding risk could be a major disadvantage.

The Panel also noted that NICE guidance 170 commented on the RECORD data noting that rivaroxaban at 10mg daily might be more efficacious than enoxaparin in preventing VTE but this was accompanied by a small increased risk of major bleeding. The NICE guidance included reference to indirect comparison of dabigatran and rivaroxaban. The Committee agreed that on balance rivaroxaban and dabigatran had broadly similar efficacy profiles and noted the need to balance prevention of VTE with possible adverse effects particularly the incidence of major bleeds.

Attached to the letter at issue was, *inter alia*, a pooled analysis of the four RECORD studies based on a presentation by Turpie (2008) and a bleeding definition paper. The RECORD studies each investigated rivaroxaban for the prevention of venous thromboembolism in patients undergoing major orthopaedic surgery vs enoxaparin. The pooled analysis concluded that for the total treatment duration significantly more bleeding was seen with rivaroxaban than enoxaparin for the combined category major bleeding plus clinically relevant non-major bleeding. The published abstract Turpie (2008) concluded, *inter alia*, that rivaroxaban was not associated with a statistically significant increase in the risk of major bleeding. The Panel noted Bayer's submission that only one of the Bayer composite endpoints for bleeding reached significance and only at a single time point that included patients receiving placebo vs rivaroxaban in RECORD 2. Boehringer Ingelheim data on file analysed the bleeding definitions and bleeding rates in the REVOLUTION study programme (Pradaxa) compared to RECORD and noted that a decision was made to change the bleeding definition for the RECORD phase III programme which could be directly responsible for the low overall events rates within the major bleeding category reported in the clinical trials.

The Panel noted that the claim 'There is some concern as to whether the superior efficacy achieved by Xarelto was at the cost of increased bleeding risk' in the letter at issue would be read as a direct comparison with Pradaxa and this was not so. The RECORD studies compared rivaroxaban with enoxaparin. There was only indirect comparative data for Pradaxa and Xarelto. The letter had not provided sufficient detail about the comparisons and was thus disparaging. A breach of Clause 8.1 was ruled.

The Panel considered that the letter by stating without further explanation that the pooled bleed data 'shows significance' over simplified the position and gave a misleading impression of the totality of the bleed data. The Panel noted that whilst further information about bleeding rates was given in the attachments to the letter at issue, the letter must be capable of standing alone with regard to the requirements of the Code. A breach of Clause 7.2 was ruled. On balance, the Panel did not consider that the reference to significance was disparaging as alleged. No breach of Clause 8.1 was ruled.

The Panel did not consider that the failure to discuss the efficacy of rivaroxaban as demonstrated in the RECORD studies was misleading or disparaging as alleged. The letter made it clear that rivaroxaban achieved superior efficacy. No breach of Clauses 7.2 and 8.1 was ruled. Consequently the Panel ruled no breach of Clause 9.1.

The Panel noted Boehringer Ingelheim's submission that medical information was rarely asked about the relative efficacy of rivaroxaban and Pradaxa. The letter referred to the balance between efficacy and bleeding it did not detail the products' relative efficacy and thus the Panel did not consider that the failure to refer to the REMOBILIZE study was misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel noted the section headed 'Epidural catheters' stated that their insertion/removal in the presence of an anticoagulant needed careful consideration and referred to an enclosed information sheet. The Panel noted that Section 4.4 of the Pradaxa SPC stated that Pradaxa was not recommended for use in patients undergoing anaesthesia with post-operative indwelling epidural catheters. The Panel noted that whilst this cautionary wording was reflected in the information which accompanied the letter, the letter had to be able to stand alone as regards the requirements of the Code. An otherwise misleading claim could not be qualified in an accompanying document. The Panel considered that given the wording of the SPC the letter was misleading about the concomitant use of catheters and the administration of Pradaxa and inconsistent with the particulars listed in its SPC. Breaches of Clauses 3.2 and 7.2 were ruled.

The Panel noted that its rulings of breaches of the Code outlined above demonstrated that the letter was, in part, inaccurate and misleading were further reasons why the letter could not take the benefit of the exemption to Clause 1.2.

The Panel noted that Bayer had also alleged a breach of Clause 9 as the letter as a whole was promotional in tone throughout and not an objective statement of medical information. The Panel considered that health professionals and others should be able to rely upon medical information departments as a source of objective information about products. The Panel noted its rulings of breaches of the Code and the Panel considered that the letter as a whole failed to maintain high standards. A breach of Clause 9.1 was ruled.

2 British Society for Haematology, 49th Annual Scientific Meeting, April 2009

COMPLAINT

Bayer alleged that Boehringer Ingelheim's stand at this meeting promoted ongoing clinical trials of dabigatran in unlicensed indications, including life

size trial logos in brand colours. Bayer alleged a breach of Clause 3.2 because it was not in accordance with the terms of the Pradaxa marketing authorization. Furthermore the safety and efficacy data for these trials were not yet available.

Bayer alleged that this provision of information about clinical trials was promotional in nature in breach of Clauses 4, 12.1 and 21.3. Having regard to this and Clause 3.2 this activity brought discredit upon the industry and was thus in breach of Clause 2. Photographs of the stand were provided.

RESPONSE

Boehringer Ingelheim stated that it had two stands at the meeting. One, which promoted Pradaxa, was set up and operated by sales and marketing. The second stand, which was the subject of this complaint, was located entirely separately within the exhibition hall and was set up and operated exclusively by medical affairs and medical information department. This second, non-promotional stand, carried no product branding and referred to only to the generic name dabigatran etexilate. It carried a clear statement of the approved indication for dabigatran and displayed study logos of the clinical studies of most interest to haematologists. Copies of the stand panels for this non-promotional stand were provided.

Boehringer Ingelheim disagreed with Bayer's allegation that the stand promoted unlicensed indications for dabigatran in breach of Clause 3.2 or that the information about clinical trials was promotional in breach of Clauses 4, 12.1 and 21.3. Boehringer Ingelheim maintained its view that the stand was appropriate and provided information on dabigatran studies to this group of health professionals in a way which complied with the Code. Haematologists were highly interested in the available data and ongoing development of oral anticoagulants in disease areas beyond VTE prophylaxis because of the burden of work that warfarin management placed upon their departments. The stand providing scientific information was set up precisely to address this anticipated demand and was located to ensure that such information was provided separately from the promotion of Pradaxa within its licensed indication. Only interested clinicians would visit and seek information. Information was provided exclusively by medical department personnel. Delegates with questions on development and clinical study matters could be directed to the medical stand from the Pradaxa promotional stand but promotional personnel were expressly forbidden from escorting the delegates to the medical stand.

Boehringer Ingelheim submitted that while the stand carried very brief information and logos for the major studies that haematologists might be interested in, it made no promotional statements about these. The personnel on the stand provided only factual scientific information related to dabigatran including information on the scope, design and progress of ongoing studies. Boehringer Ingelheim strongly believed that this provided a scientifically valid and useful service for these clinicians that was not promotion of dabigatran. The logos and text displayed on the stand and the information that was provided in response to enquiries was, in Boehringer Ingelheim's view, directly comparable to the information provided to health professionals through the medium of a sponsored scientific symposium. The Bayer allegation that this constituted promotion of an unlicensed indication was unsustainable.

PANEL RULING

The Panel noted that the Code did not prevent the legitimate exchange of medical and scientific information during the development of a medicine provided that any such information or activity did not constitute promotion prohibited by Clause 3 or any other clause. In the Panel's view companies needed to be particularly careful when providing medical and scientific information about unlicensed indications.

The Panel noted that Boehringer Ingelheim had two stands, one that was clearly promotional and the stand at issue which was located entirely separately in the exhibition hall. The actual meeting was run by the British Society for Haematology; Boehringer Ingelheim like many companies had paid for exhibition space.

The Panel noted that the exhibition stand at issue presented information about the REVOLUTION clinical trial programme: acute VTE treatment; secondary VTE prevention; SPAF and secondary prevention of cardiac events in patients with acute coronary syndrome. The Panel noted the submission that the stand had been set up to meet an anticipated demand for information beyond VTE prevention. The Panel disagreed with the submission that only interested physicians would visit and seek information. The stand panels included a section listing features of dabigatran, a reference to what appeared to be a Boehringer Ingelheim meeting 'A Question of Anticoagulation' and stated that medical information was available on request. In the Panel's view such a statement would solicit requests. Boehringer Ingelheim submitted that the logos used on the stand were for the clinical studies mentioned and no product branding was included. The stand was manned by medical affairs and medical information staff. Boehringer Ingelheim had provided the briefing document to the sales team regarding UK congresses which stated that the REVOLUTION stand was used in addition to the normal branded stand pre-launch.

The Panel was concerned about the stand; its presence demonstrated a poor understanding of the requirements of the Code. The Panel noted that the supplementary information to Clause 1.2 provided relevant guidance stating that a solicited enquiry would be one where a company invited a person to

make a request. Placing documents on an exhibition stand amounted to an invitation to take them. The Panel considered that the exhibition stand at issue solicited enquiries about dabigatran and the REVOLUTION clinical trial programme. The Panel noted that Pradaxa was licensed for the primary prevention of VTE following elective total hip or total knee replacement surgery. The Panel considered that the exhibition stand promoted Pradaxa for unlicensed indications and this was inconsistent with the SPC. A breach of Clause 3.2 was ruled. As Pradaxa was promoted prescribing information needed to be provided or made available at the stand. A breach of Clause 4.1 was ruled. The Panel did not consider that the promotional activity was disguised as alleged. No breach of Clause 12.1 was ruled. The Panel did not consider that the stand at issue represented a failure to disclose details of clinical trials as required by Clause 21.3. The supplementary information to that clause reminded companies that such information must not constitute promotion. That aspect was covered by the Panel's rulings outlined above. No breach of Clause 21.3 was ruled.

Although seriously concerned about the stand, on balance the Panel did not consider that a ruling of a breach of Clause 2 was warranted. This was reserved for use as a sign of particular censure. No breach of Clause 2 was thus ruled.

Complaint received **18 May 2009**

Case completed **14 September 2009**