CASE AUTH/2490/3/12

VOLUNTARY ADMISSION BY BAYER HEALTHCARE

Conduct of an employee

Bayer Healthcare voluntarily admitted that a healthcare development consultant (HDC) had prepared and used three documents which related to Xarelto (rivaroxaban) without the company's knowledge or approval. In accordance with Paragraph 5.6 of the Authority's Constitution and Procedure, the Director treated the matter as a complaint. Xarelto was a non-vitamin K antagonist oral anticoagulant.

Bayer stated that a service improvement manager for an NHS heart and stroke network had written to the company outlining a number of concerns about a proposal for joint working she had received from the HDC. Bayer submitted that the documents given by the HDC to the service improvement manager raised a number of very serious concerns about the proposal, namely; it was promotional; the 'costs and claims' were not 'accurate and approved by Bayer'; the 'comparative claims' were not 'accurate, fair and based on data'; reference was made to 'future indications' and 'out of licence claims'; it did not comply with the Code and guidance for joint working. In view of the above, Bayer admitted multiple breaches of the Code.

Bayer submitted that the subsequent investigation revealed that the HDC had worked on two projects. The first was with the medicines management team to help develop a business case for rivaroxaban to be included on the formulary for the primary care trust (PCT). The second project was with the service improvement manager on the development of a patient access pathway for the introduction of the new non-vitamin K antagonist oral anticoagulants. The HDC sent the service improvement manager a copy of the business case for information along with the project initiation document and the draft patient access pathway. It was the content of these documents that prompted the service improvement manager to complain to Bayer. The three documents were developed and distributed entirely at the HDC's own initiative and unbeknown to Bayer; they were not submitted for review and certification.

The detailed response from Bayer is given below.

The Panel noted that other than the documents at issue and a copy of the Xarelto 15mg summary of product characteristics (SPC) Bayer had not supplied copies of any references in support of its admissions. The Panel thus relied upon Bayer's admissions when it made its rulings.

The Panel noted that none of the documents at issue had been approved for use by Bayer; they had been developed and distributed entirely on the initiative of the HDC. The Panel noted, however, that a previous draft of the rivaroxaban business case was first seen by the HDC's line manager (a regional business manager (RBM)) in October 2011. The document was further discussed in January 2012 at a sales meeting. On the first occasion the HDC was reminded by the RBM about the need for the document to be approved and on the second occasion the national sales manager stressed the need for certification to both the RBM and the HDC. There was no follow-up on either occasion from the RBM to check that the necessary action had been taken. In the Panel's view this was wholly unacceptable particularly given the discussion of the document in January 2012 – three months after the RBM had first reminded the HDC about the need for approval.

The Panel noted that a service improvement manager had been sent a package of information to support the introduction and use of rivaroxaban. The Panel considered that the documents had thus all been sent to promote the prescription of rivaroxaban and were promotional in nature. The documents had not been certified and a breach of the Code was ruled. It was not clear that Bayer had originated the documents and in that regard the Panel considered that they were disguised promotion and ruled a breach of the Code. The documents contained no prescribing information, no reference to adverse event reporting and no inverted black triangle. Breaches of the Code were ruled. All of the above breaches of the Code were acknowledged by Bayer.

The Panel noted that the rivaroxaban business case contained many statements that were misleading with regard to the licensed indication for the medicine, the requirement for patient monitoring, interactions with food and/or concomitant medicines, the safety and cost effectiveness of rivaroxaban. Breaches of the Code were ruled. The Panel further noted that the business case also contained a number of hanging comparisons and statements that could not be substantiated. Breaches of the Code were ruled. Misleading comparisons of rivaroxaban with competitor medicines were made. Breaches of the Code were ruled. In addition, reference was made to a future indication for rivaroxaban. A breach of the Code was ruled. All of the above breaches of the Code were acknowledged by Bayer.

The Panel noted that the project initiation document, which appeared to be a joint working proposal, set out a pilot patient access pathway for the introduction of a non-vitamin K antagonist oral anticoagulant (rivaroxaban). External support for one day a week would be provided to support the project. The Panel considered that the proposal was in effect an inducement to prescribe rivaroxaban. The Panel considered that the document was

unbalanced and a breach of the Code was ruled as acknowledged by Bayer.

The Panel noted that the draft patient pathway referred to arterial fibrillation, not atrial fibrillation. The Panel also noted Bayer's submission that the pathway was not accurate and was misleading. The Panel ruled a breach of the Code as acknowledged by Bayer.

The Panel noted that the documents at issue were very poor quality and had been produced outside of the company's approval process and circulated to a number of health professionals by the HDC. A breach of the Code was ruled with regard to the failure of the HDC to maintain high standards. The Panel noted its rulings above and its concerns with regard to the poor management of the HDC. In that regard the Panel considered that the company had not maintained high standards and a breach of the Code was ruled.

The Panel considered that the circulation, albeit limited, of such poor quality documents which contained multiple errors, including misleading statements with regard to patient safety, was such as to bring discredit upon or reduce confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2.

Bayer Healthcare voluntarily admitted that a Healthcare Development Consultant (HDC) (employed on contract through a third party) had prepared and used three documents which related to Xarelto (rivaroxaban) without the company's knowledge or approval. In accordance with Paragraph 5.6 of the Authority's Constitution and Procedure, the Director treated the matter as a complaint.

Xarelto was a non-vitamin K antagonist oral anticoagulant.

COMPLAINT

Bayer stated that in February 2012, it received a letter from a service improvement manager for an NHS heart and stroke network (a clinical network hosted by the NHS) which outlined a number of concerns about a proposal for joint working. The service improvement manager referred to the following three documents which had been given to her by the HDC:

- project initiation document: a pilot for a patient access pathway
- draft patient access pathway for atrial fibrillation (AF)
- rivaroxaban business case.

Bayer provided copies of the documents and submitted that they raised a number of very serious concerns about the proposal, namely:

- It was promotional; it should not 'point a pathway in favour of pharmaceutical products or be contingent on formulary inclusion'.
- The 'costs and claims' were not 'accurate and approved by Bayer'.
- The 'comparative claims' were not 'accurate, fair and based on data'.
- Reference to 'future indications' and 'out of licence claims'.
- It did not comply with the Code and guidance for joint working.

In view of the above, Bayer admitted breaches of Clauses 3.1, 4.1, 4.10, 4.11, 7.2, 7.3, 12.1, 14.1, 15.2 and 9.1.

Bayer submitted that the subsequent investigation revealed that the HDC had worked on two projects. The first was with the medicines management team to help develop a business case for rivaroxaban to be included on the formulary for the primary care trust (PCT). The rivaroxaban business case was sent to two members of the medicines management team, a formulary development pharmacist and a GP who sat on the formulary advisory board.

The second project was with the service improvement manager on the development of a patient access pathway for the introduction of the new non-vitamin K antagonist oral anticoagulants. The HDC had a good working relationship with the service improvement manager and sent her a copy of the business case for her information along with the project initiation document and the draft patient access pathway. It was the content of these documents that prompted the service improvement manager to complain to Bayer. The three documents were developed and distributed entirely at the HDC's own initiative and unbeknown to Bayer; they were not submitted for review and certification.

Bayer submitted that the review and approval process for marketing and educational materials/activities was defined by a Bayer standard operating procedure (SOP) which clearly stated that all promotional items, non-promotional items and proposals for activities must be certified according to the Code.

Bayer had trained and validated the HDC on the requirements of the Code and the company's relevant SOPs. Bayer provided details of the HDC's ABPI Medical Representatives Examination status. Bayer submitted that despite the appropriate training, the HDC initiated and distributed the unapproved documents with disregard for the requirements of the Code, the ABPI guidance on joint working and Bayer internal policies.

As a result the HDC was immediately suspended and subsequently his/her contract was terminated. In addition Bayer noted that it had had a face-to-face meeting with the service improvement manager in March 2012 to address her concerns and to give a full and accurate account of the events together with the subsequent actions. At the meeting Bayer emphasised that it took this matter seriously and that a voluntary admission would be made to the PMCPA.

The service improvement manager stated that, despite this regrettable incident, she was still keen to enter into joint working with Bayer.

Bayer regarded the HCD's failure to apply his/her training and follow company procedures designed to ensure compliance with the Code, as a serious matter, hence its voluntary admission. Bayer trusted that the Authority would regard the actions that it had taken to address, what it believed to be, an isolated incident as satisfactory.

The Authority wrote to Bayer seeking further information and asked for its comments in relation to Clause 2 of the Code in addition to those clauses referred to above.

RESPONSE

Bayer's concerns with regard to the HDC's activities in terms of Clause 2 were mainly related to the unlicensed indications mentioned in the business case document, and therefore patient safety. However, there was never any question that this joint working project, in the early draft form proposed by the HDC, would have gone ahead. The national sales manager knew of the proposed project and was acutely aware that joint working projects and all associated documents had to be certified in accordance with Bayer SOPs on certification and joint working. These SOPs were designed to ensure compliance with the Code, the ABPI Guidance Notes on Joint Working between Pharmaceutical Companies and the NHS and Others for the Benefit of Patients and the Department of Health 'NHS Best Practice Guidance on Joint Working'.

Bayer considered that its actions to address this matter, together with its voluntary admission, were sufficient testimonial to its compliance culture as well as commitment to self-regulation and that therefore it had not brought the industry into disrepute.

Bayer explained that the HDC and the service improvement manager had discussed a proposal for a patient access pathway to help with the introduction and prescribing of non-vitamin K antagonist anticoagulants. In these preliminary discussions the HDC developed and used the project initiation document in conjunction with the draft patient access pathway for atrial fibrillation, on which the pilot patient access pathway was outlined. The documents were used for preliminary discussions around the project and apparently the HDC intended to get them certified once both parties had agreed the details of the project. The HDC therefore fundamentally misunderstood the certification requirements of the Code.

At the same time the HDC had also discussed a formulary application with the medicines management team at this particular trust. The HDC had developed the uncertified rivaroxaban business case document to use in these discussions to outline the rationale for Xarelto to be included on the trust formulary.

The HDC sent to the service improvement manager, for her feedback and comment, the project initiation and patient access documents which had been used in their discussions. The rivaroxaban business case was, in the words of the HDC, 'sent in what I believed to be the interests of transparency'; he/she thought it might be useful background information.

The HDC sent all three documents to two members of the medicines management team, a formulary development pharmacist and a GP who sat on the formulary advisory board.

It was subsequently discovered that the HDC had emailed copies of the rivaroxaban business case to three other HDCs. Bayer stated that they had not discussed or distributed these documents either internally or externally, and the electronic copies had been destroyed.

Bayer submitted that none of the three documents had been certified, in breach of Clause 14.1, and none contained the required prescribing information, adverse event reporting statement or black triangle in breach of Clauses 4.1, 4.10 and 4.11 respectively.

Bayer submitted that the documents were disguised promotion in breach of Clause 12.1.

With regard to the content of the rivaroxaban business case document, Bayer noted the following:

- 'Prevention of DVT [deep vein thrombosis] post hip or knee replacement surgery in adults', or similar.

This was not accurate in breach of Clause 7.2. The correct statement would be 'prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery'.

- 'The use of Rivaroxaban in AF [atrial fibrillation] patients for the prevention of stroke'.

This was not accurate and was misleading in breach of Clause 7.2. The correct statement should be 'Prevention of stroke and systemic embolism in eligible adult patients with non-valvular atrial fibrillation'.

- 'Both Warfarin and LMWH [low molecular weight heparin] may well be affected by compliance, concordance and side effect issues thus reducing the clinical effectiveness of the management regimen.'

Although it was true that compliance, concordance and side effects could be an issue with these medicines Bayer could not substantiate the claim that clinical effectiveness was reduced as a result. This was also unbalanced as it did not mention any issues which might arise with the use of rivaroxaban. Therefore this statement was in breach of Clauses 7.2 and 7.4.

- 'Rivaroxaban is an oral once daily anticoagulant (direct Factor Xa inhibitor) having a fixed dose regime, requires no monitoring, has low drug-drug interactions and an improved safety profile'.

Bayer submitted that this was not accurate and was misleading as it implied that patients on rivaroxaban required no monitoring whereas they would need to be monitored in a general sense. What should have been stated was 'no routine anticoagulation monitoring'. This statement also contained a hanging comparison as it referred to an improved safety profile but did not state in comparison to what. Therefore this statement was in breach of Clause 7.2.

- 'No Monitoring: reducing direct and indirect cost and resource pressure on Warfarin clinics and patients. Thus releasing capacity'.

Bayer submitted that it was not acceptable to say 'no monitoring' for the reasons outlined above. As this statement stood it was not sufficiently complete and would require further quantification, it was therefore in breach of Clause 7.2.

- 'Response profile is not influenced by diet, concomitant medications, age or ethnicity'.

Bayer stated that this was not accurate and was misleading as both the 15mg and 20mg doses had to be taken with food, it was only the 10mg dose that did not need to be taken with food. Also rivaroxaban was potentially influenced by concomitant medicines. Therefore this statement was in breach of Clause 7.2.

- 'Greater patient empowerment'

Bayer submitted that this statement was not capable of substantiation and therefore in breach of Clause 7.4.

- All of the the statements under the heading 'Outline benefits to:'

Bayer submitted that these were hanging comparisons. The statement 'Reduced risk of significant event owing to reductions in TTR' [time in therapeutic range] could not be substantiated. All the statements under the sub-heading 'Local Health Economy' were also hanging comparisons and were not capable of substantiation. Bayer therefore submitted that these sections were in breach of Clauses 7.2 and 7.4.

- 'Management of this "at greater risk population" will reduce the burden on the local healthcare economy in both direct and indirect social care/economic impact costs associated with TIA, [transient ischaemic attack] Stroke, DVT, PE [pulmonary embolism] and AF'.

Bayer submitted that this statement could not be substantiated and was in breach of Clause 7.4.

- 'Rivaroxaban shows superiority over enoxaparin a convenient administrative schedule (following epidural) and clinical use (mild/moderate renal impairment)'

Bayer submitted that this was shown in the referenced study (Grosso and Bodalia 2009) however it was unbalanced and therefore in breach of Clause 7.2. To provide a balanced overview more information should have been included. Quotations from the study included:

> 'The dosing schedule for rivaroxaban is more simple than that of dabigatran and is more appropriate for patients undergoing surgery with an epidural.'
>
> 'Since rivaroxaban also appears more convenient in both its administrative schedule (following epidural) and clinical use (in mild/ moderate renal impairment), the University College London Hospitals NHS Foundation Trust Use of Medicines Committee approved the use of rivaroxaban in place of LMWH for extended thromboprophylaxis after THR [total hip replacement] and TKR [total knee replacement] surgery.'
>
> 'Rivaroxaban has an advantage over dabigatran since it can be used in patients with a creatinine clearance of 15–30ml/minute (with caution, based on limited clinical data).'

- 'Intracranial and fatal bleeding occurred less frequently in the Rivaroxaban group'.

Bayer stated that although this statement was true and could be substantiated it did not provide a balanced overview of the data, it was misleading and a hanging comparison in breach of Clause 7.2. It should have been stated that there were more gastrointestinal (GI) bleeds in the rivaroxaban group compared with warfarin.

- This section included information on potential future indications for rivaroxaban (prevention of thromboembolic events in patients with acute coronary syndrome and treatment of symptomatic pulmonary embolism), and was therefore in breach of Clause 3.1. This information appeared in Section 1.5 and the table in Section 2.7.

- 'In patients with recent acute coronary syndrome, rivaroxaban reduced the risk of the composite endpoint of death from cardiovascular causes, myocardial infarction or stroke'

Bayer submitted that this statement was true, but only part of the quotation from the referenced study (Husten 2011) was used. The quotation from Husten also stated: 'Rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding'. By leaving out the second sentence it was misleading and not balanced and therefore in breach of Clause 7.2.

- 'Rivaroxaban requires no monitoring or dose adjustments'.

Bayer stated that the statement regarding dose adjustments was true for the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery (10mg dose). However, for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation and for the treatment of DVT, and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults, the claim was misleading and not accurate, as dose adjustments were required for renally impaired patients. Bayer also referred to its comments above about monitoring. This statement was therefore in breach of Clause 7.2.

- 'Rivaroxaban has been demonstrated to be cost effective in a number of studies across the orthopaedic indication dominating enoxaparin including in the UK setting using life LYs and QALYs [quality adjusted life years] as measures'

Bayer stated that this statement did not accurately reflect the references (McCullagh *et al* 2009 and Hamidi *et al* 2011) and was therefore in breach of Clause 7.2. McCullagh *et al* actually stated: 'Base-case analysis indicates that when both rivaroxaban and dabigatran etexilate are compared with enoxaparin sodium, rivaroxaban is the less costly and more effective option after THR and TKR. Probabilistic sensitivity analysis indicates that rivaroxaban is the most cost-effective strategy at a cost-effectiveness threshold of €45,000 per QALY; however, there is uncertainty regarding this strategy being more cost effective than dabigatran etexilate when both are compared with enoxaparin sodium'.

- 'Dabigatran has been reported to be associated with a higher risk of acute coronary events'.

Bayer submitted that this was a hanging comparison and required further quantification and explanation, and was therefore in breach of Clause 7.2.

- The table comparing rivaroxaban with dabigatran.

Bayer submitted that the table contained incomplete information and was therefore unbalanced and misleading in breach of Clauses 7.2 and 7.3. The following information should have been presented:

Class, Posology & Administration: For the prevention of stroke and systemic embolism the recommended dose is 20mg once daily, which is also the recommended maximum dose. The recommended dose for the initial treatment of acute DVT is 15mg twice daily for the first three weeks followed by 20mg once daily for the continued treatment and prevention of recurrent DVT and PE.

Renal impairment: No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50-80ml/min). In patients with moderate (creatinine clearance 30-49ml/min) or severe (creatinine clearance 15-29ml/min) renal impairment the following dosage recommendations apply:

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15mg once daily.

- For the treatment of DVT and prevention of recurrent DVT and PE: Patients should be treated with 15mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 15mg once daily based on pharmacokinetic modeling.

Limited clinical data for patients with severe renal impairment (creatinine clearance 15-29ml/min) indicate that rivaroxaban plasma concentrations are significantly increased therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15ml/min.'

Bayer further noted that the section entitled 'Key Drug-Drug interactions/cautions' had been left blank for rivaroxaban which was misleading as it implied there were no interactions with other medicines or cautions.

Bayer also submitted that the section of the table entitled 'Licence indications CHMP [Committee for Medicinal Products for Human Use] and/or NICE [National Institute for Health and Clinical Excellence] approval' was not clear and was ambiguous about which indication was CHMP approved and which had NICE approval. Rivaroxaban was recommended by NICE for the orthopaedic indication but not for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation or the treatment of DVT, and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

Turing to the project initiation document, Bayer submitted that it was unbalanced as it referred only to the use of rivaroxaban, whereas this type of project should include all available therapeutic options for this patient group. The document was therefore in breach of Clause 7.2.

Bayer noted that the draft patient access pathway referred to 'Arterial Fibrillation' which was not accurate; it was 'Atrial Fibrillation'. In addition the flow was not accurate and was misleading, and therefore in breach of Clause 7.2.

Bayer explained that the HDC's line manager (regional business manager (RBM)) was the first person to see the rivaroxaban business case in October 2011. That version was an earlier draft of the document received by the service improvement manager. The RBM did not see the project initiation or the patient access documents until after the service improvement manager had complained.

No one else at Bayer saw the documents until after the complaint had been made by the service improvement manager.

Bayer submitted that when the RBM first saw the rivaroxaban business case in October 2011 he expressed concerns and asked the HDC if it had been submitted for approval. The RBM was assured by the HDC that it was 'under medical review'. The RBM did not check to see if this was the case. Bayer noted that the rivaroxaban business case was never submitted for approval.

Bayer stated that the rivaroxaban business case was discussed at a sales meeting on 9 January 2012. The national sales manager (the RBM's line manager) stressed to both the HDC and the RBM that that document and any others associated with it would have to be certified as soon as possible, and specifically before the project went any further. However no specific actions, follow-up or timelines were put in place to ensure that this was done. Nevertheless the HDC role was a senior one and ordinarily these individuals should not require such close supervision.

Bayer stated that its SOP on the internal process for the initiation and conduct of a joint working project clearly stated that all materials and activities associated with joint working must be certified in accordance with its certification process (ie all promotional items, non-promotional items and proposals for activities must be certified according to the Code).

Bayer submitted that in terms of formulary applications there was no set process as it was a sales process and would differ slightly in every health economy in the UK. Trusts and PCTs often produced their own guidelines for formulary applications, and in these cases the guidance was strictly followed. However the consistent principle was that the Code was followed throughout and in particular compliance with its certification process.

PANEL RULING

The Panel noted that other than the documents at issue and a copy of the Xarelto 15mg summary of product characteristics (SPC) Bayer had not supplied copies of any references in support of its admissions. The Panel thus relied upon Bayer's admissions when it made its rulings.

The Panel noted that none of the documents at issue had been approved for use by Bayer; they had been developed and distributed entirely on the initiative of the HDC. The provision of these documents had prompted a service improvement manager to complain to Bayer. It appeared that the documents had been provided to the service improvement manager in February 2012. The Panel noted, however, that a previous draft of the rivaroxaban business case was first seen by the HDC's line manager (an RBM) in October 2011. The document was further discussed in January 2012 at a sales meeting. On the first occasion the HDC was reminded by the RBM about the need for the document to be approved and on the second occasion the national sales manager stressed the need for certification to both the RBM and the HDC. There was no follow-up on either occasion from the RBM to check that the necessary action had been taken. In the Panel's view this was wholly unacceptable particularly given the discussion of the document in January 2012 – three months after the RBM had first reminded the HDC about the need for approval. The Panel noted Bayer's submission that the seniority of the HDC role suggested that close supervision was not necessary. In the Panel's view, however, the repeated internal discussion of the business case document by the HDC concerned should have alerted senior managers otherwise.

The Panel noted that a service improvement manager had been sent a package of information to support the introduction and use of rivaroxaban. The business case document stated that the aim of the document was to provide evidential support for the adoption of rivaroxaban onto the local formulary. The project initiation document stated that the project would, *et al*, provide a clear and unambiguous access pathway to rivaroxaban. The patient pathway document did not refer to rivaroxaban specifically but appeared to be an integral part of the package. The Panel considered that the documents had all been sent to promote the prescription of rivaroxaban and were thus promotional in nature. The documents had not been certified and a breach of Clause 14.1 was ruled. It was not clear that Bayer had originated the documents and in that regard the Panel considered that they were disguised promotion and ruled a breach of Clause 12.1. The documents contained no prescribing information, no reference to adverse event reporting and no inverted black triangle. The Panel ruled breaches of Clauses 4.1, 4.10 and 4.11 respectively. All of the above breaches of the Code were acknowledged by Bayer.

Turning to the content of the rivaroxaban business case, the Panel noted that there were several references to the medicine being licenced to prevent DVT post hip or knee replacement surgery. Rivaroxaban was in fact licensed to prevent VTE which included not only DVT but also pulmonary embolus. The Panel considered that the claims were incorrect as acknowledged by Bayer. A breach of Clause 7.2 was ruled.

Page one of the business case referred to 'The use of Rivaroxaban in AF patients for the prevention of stroke'. The Panel noted that rivaroxaban was licensed for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors. The Panel thus considered that the statement in the business case document was inaccurate and misleading. A breach of Clause 7.2 was ruled as acknowledged by Bayer.

The Panel noted Bayer's submission that the statement that 'Both Warfarin and LMWH may well be affected by compliance, concordance and side effect issues thus reducing the clinical effectiveness

of the management regimen' could not be substantiated and that there was no comparable reference to issues which might arise with rivaroxaban. The Panel thus considered that the statement was unbalanced and unsubstantiable. Breaches of Clauses 7.2 and 7.4 were ruled as acknowledged by Bayer.

The Panel noted that the business case stated that rivaroxaban required no monitoring; it was unclear as to what that meant. The SPC stated that clinical surveillance in line with anticoagulation practice was recommended throughout the treatment period and Bayer had submitted that patients would have to be monitored in the general sense. The Panel considered that references to 'no monitoring' were thus misleading as acknowledged by Bayer. A breach of Clause 7.2 was ruled.

The Panel noted the claim that 'Rivaroxaban….has… .an improved safety profile'. It was not stated that with which the medicine was compared. The claim was thus a hanging comparison as acknowledged by Bayer and the Panel ruled a breach of Clause 7.2.

The Panel noted that the business case stated that the response profile of rivaroxaban was not influenced by, *et al*, diet and/or concomitant medications. This was not so. Doses of rivaroxaban above 10mg had to be taken with food in order to increase its bioavailability. Further, Section 4.5 of the Xarelto 15mg SPC, interaction with other medicinal products and other forms of interaction, stated that co-administration of some medicines (eg ketoconazole or ritonavir) would increase the bioavailabilty of rivaroxaban whilst the co-administration of others (eg rifampicin) would decrease its bioavailability. The Panel considered that the claim at issue was inaccurate and misleading as acknowledged by Bayer. A breach of Clause 7.2 was ruled.

The business case document stated that one of the benefits of treatment for the patient was 'Greater patient empowerment'. The Panel noted Bayer's submission that this claim could not be substantiated. A breach of Clause 7.4 was ruled.

The Panel noted that Section 1.4 of the business case document contained the following hanging comparisons; 'Greater patient empowerment'; 'Better care…'; 'Fewer admission…'; '…fewer medicine related adverse events….; '…better medicines management' and 'Better use of resources…'. The Panel ruled a breach of Clause 7.2 in each case as acknowledged by Bayer. The same section of the document also contained the statement 'Reduced risk of significant event owing to reductions in TTR [time in therapeutic range]' which Bayer had submitted could not be substantiated. The company had also submitted that the four statements under the heading 'Local Health Economy' could not be substantiated. The Panel thus ruled each statement in breach of Clause 7.4.

The Panel noted Bayer's submission that the statement 'Management of this "at greater risk population" will reduce the burden on the local healthcare economy in both direct and indirect social care/economic impact costs associated with TIA, Stroke, DVT, PE and AF' could not be substantiated. The Panel thus ruled a breach of Clause 7.4.

The Panel noted Bayer's submission that the claim 'Rivaroxaban shows superiority over enoxaparin a convenient administrative schedule (following epidural) and clinical use (mild/moderate renal impairment)' was unbalanced in breach of Clause 7.2. The claim was referenced to Grosso and Bodalia which was a study of dabigatran vs rivaroxaban for thromboprophylaxis. It was not a comparison of rivaroxaban and enoxaparin as implied by the claim. The Panel considered that the claim was thus misleading. A breach of Clause 7.2 was ruled.

The Panel noted that beneath a heading of 'Rivaroxaban versus Warfarin in Non-Valvular Atrial Fibrillation' was the claim 'Intracranial and fatal bleeding occurred less frequently in the Rivaroxaban group'. Bayer had submitted that this claim was a hanging comparison but the Panel considered that, given the heading, it was clear as to with what rivaroxaban was compared. No breach of Clause 7.2 was ruled in that regard. The Panel further noted Bayer's submission that there were more GI bleeds in the rivaroxaban group compared with the warfarin group. Given the reference to bleeding risk the Panel considered that it was misleading and unbalanced to refer to the favourable results for intracranial and fatal bleeding but not to the unfavourable results for GI bleeding. A breach of Clause 7.2 was ruled.

The Panel noted that the business case document referred to future indications for rivaroxaban, ie acute coronary syndrome. Rivaroxaban did not have a marketing authorization for acute coronary syndrome and so in that regard the Panel ruled a breach of Clause 3.1 as acknowledged by Bayer. The Panel further noted Bayer's submission that the claim 'In patients with recent acute coronary syndrome, rivaroxaban reduced the risk of the composite endpoint of death from cardiovascular causes, myocardial infarction or stroke' was referenced to Mega *et al* (2011). The Panel noted Bayer's submission that this was misleading in breach of Clause 7.2 as it did not refer to the increased risk with rivaroxaban of major bleeding and intracranial hemorrhage also seen in this study. The Panel considered that the claim was misleading as acknowledged by Bayer; a breach of Clause 7.2 was ruled.

The business case document contained the claim 'Rivaroxaban requires no monitoring or dose adjustments'. The Panel noted that this was not so for all patients, eg Section 4.2 of the Xarelto 15mg SPC, Posology and method of administration, stated that for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the daily dose of rivaroxaban should be decreased from 20mg to 15mg in those with moderate to severe renal impairment. In addition the Panel noted its comments and rulings about in relation to references to no monitoring. The Panel

considered that the claim was misleading as acknowledged by Bayer. A breach of Clause 7.2 was ruled.

The Panel noted Bayer's submission that the claim 'Rivaroxaban has been demonstrated to be cost effective in a number of studies across the orthopaedic indication dominating enoxaparin including in the UK setting using life LYs and QALYs as measures' was not accurate; it appeared that one of the references cited in support of the claim (McCullagh *et al*) was more equivocal in its conclusion. A breach of Clause 7.2 was ruled.

The Panel noted that the business case contained the claim 'Dabigatran has been reported to be associated with a higher risk of acute coronary events'. Dabigatran was a competitor product to rivaroxaban (marketed by Boehringer Ingelheim). The Panel considered that within the context of a business case document for rivaroxaban, it would be clear that dabigatran was being compared with rivaroxaban. In that regard the Panel did not consider that the claim was a hanging comparison as stated by Bayer and no breach of Clause 7.2 was ruled.

The Panel noted Bayer's submission that there were multiple omissions in a table of data comparing rivaroxaban with dabigatran. The Panel noted that the data regarding class, posology and administration was incomplete; the data on renal impairment was limited and there was no data at all given for rivaroxaban with regard to key drug-drug interactions/cautions. The information stated with regard to which indications had been approved by NICE was ambiguous. The Panel considered overall that the table of data and the comparisons within were misleading. Breaches of Clause 7.2 and 7.3 were ruled.

The Panel noted that the project initiation document, which appeared to be a joint working proposal, set out a pilot patient access pathway for the introduction of a non-vitamin K antagonist oral anticoagulant (rivaroxaban). External support for one day a week would be provided to support the project. The Panel considered that the proposal was in effect an inducement to prescribe rivaroxaban although there were other oral anticoagulants in the same class. Given the lack of reference to the other medicines in the same class the Panel considered that the document was unbalanced and a breach of Clause 7.2 was ruled as acknowledged by Bayer.

The Panel noted that the draft patient pathway referred to arterial fibrillation, not atrial fibrillation. The Panel also noted Bayer's submission that the pathway was not accurate and was misleading. The Panel ruled a breach of Clause 7.2 as acknowledged by Bayer.

The Panel noted that the documents at issue were very poor quality and had been produced outside of the company's approval process and circulated to a number of health professionals by the HDC. A breach of Clause 15.2 was ruled with regard to the failure of the HDC to maintain high standards. The Panel noted its rulings above and its concerns with regard to the poor management of the HDC. In that regard the Panel considered that the company had not maintained high standards and a breach of Clause 9.1 was ruled.

The Panel considered that the circulation, albeit limited, of such poor quality documents which contained multiple errors, including misleading statements with regard to patient safety, was such as to bring discredit upon or reduce confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2.

Complaint received **14 March 2012**

Case completed **25 May 2012**