ANONYMOUS v BAYER

Promotion of Xarelto

An anonymous, non-contactable complainant complained about a two page advertisement published in GP, 24 October 2012, for Xarelto (rivaroxaban) issued by Bayer HealthCare. Xarelto was an oral anticoagulant. The advertisement referred, *inter alia*, to the use of Xarelto for stroke prevention in atrial fibrillation (AF) and in that regard stated 'one tablet, once daily, simple'.

The complainant's view was that the advertisement was outrageous. Xarelto, like all anticoagulants, carried a risk of bleeding which could be severe or even fatal. The use of all anticoagulants needed to be considered and monitored with care.

The claim that Xarelto was 'simple' to use did not accurately reflect the inherent risks with this class of medicine nor was it consistent with the prescribing information which did not seem to support that this was a simple medicine to use. There were cautions and/or dose reductions in renal impairment and the 'Contraindications', 'Warnings and Precautions' and 'Interactions' sections were extensive, complex and covered a wide range of situations and circumstances.

The complainant alleged that advertising the use of such a medicine as 'simple' was likely to encourage inadequately considered or even inappropriate use with a consequent impact on patient safety.

The detailed response from Bayer is given below.

The Panel noted that it was clear that the reference to simple was in relation to the indication for stroke prevention in AF. It was also clear that 'simple' referred to the dosing regimen, as it appeared in the phrase 'one tablet, once daily, simple'. It was not a claim that generally Xarelto was simple to use.

The Panel considered that readers of the advertisement (GPs and health professionals working in primary care) would be aware of the complexities associated with the use of warfarin. It noted Bayer's submission regarding the need to monitor and adjust the doses of warfarin. Sections 4.4 and 5.1 of the Xarelto 20mg summary of product characteristics (SPC) stated that there was no need for the monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated, rivaroxaban levels could be measured by certain tests. Section 4.4 of the SPC stated that 'Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period'.

The Panel noted the recommended dose of Xarelto in the prevention of stroke and systemic embolism in patients with AF and certain risk factors was 20mg per day. Therapy was to be continued long-term provided the benefit of prevention of stroke and systemic embolism outweighed the risk of bleeding. Dose adjustment was needed in patients with renal impairment.

The Panel did not consider there was a general claim that Xarelto was simple to use as alleged. 'Simple' was used to describe the dosing regimen. The dosing regimen for Xarelto was not as complicated as for other products in this therapeutic area and in this context the broad indication of one tablet once a day for a number of patient populations might be viewed as simple.

The Panel did not consider that the claim 'one tablet, once daily, simple' was inconsistent with the SPC. Nor was the claim an inaccurate reflection of the risks of using anticoagulants as alleged. Given the above the Panel did not consider the company had failed to maintain high standards nor had it brought discredit to or reduced confidence in the pharmaceutical industry. No breaches of the Code, including no breach of Clause 2, were ruled.

An anonymous, non-contactable complainant complained about a two page advertisement (ref L.GB.09.2012.0568h) for Xarelto (rivaroxaban) issued by Bayer HealthCare. Xarelto was an anticoagulant. The advertisement, which was published in GP, 24 October 2012, referred, *inter alia*, to the use of Xarelto for stroke prevention in atrial fibrillation (AF) and in that regard stated 'one tablet, once daily, simple'.

COMPLAINT

The complainant stated that in his/her view the advertisement was outrageous. Xarelto was an oral anticoagulant which, like all anticoagulants, carried an attendant risk of bleeding which could be severe or even fatal. The use of all anticoagulants needed to be considered and monitored with care.

The complainant noted that the advertisement indicated that Xarelto was 'simple' to use which, in his/her view, did not accurately reflect the inherent risks with this class of medicine nor was it consistent with the prescribing information. The prescribing information certainly did not seem to support that this was a simple medicine to use. There were cautions and/or dose reductions in renal impairment and the 'Contraindications', 'Warnings and Precautions' and 'Interactions' sections were very extensive, quite complex and covered a wide range of situations and circumstances.

The complainant alleged that advertising the use of such a medicine as 'simple' was likely to encourage

inadequately considered or even inappropriate use with consequent impact on patient safety.

When writing to Bayer, the Authority asked it to consider the requirements of Clauses 2, 3.2, 7.2, 7.9 and 9.1.

RESPONSE

Bayer explained that before the introduction of this latest class of anticoagulants, referred to in the literature as novel oral anticoagulants (NOACs), there were two main treatment options, injectable anticoagulants such as heparin and oral medicines vitamin K antagonists like warfarin.

Heparins required dose adjustment by weight and needed to be administered at least once a day. Injections might result in extensive bruising, stress of needle prick, pain and discomfort. Self-injection required dexterity which not all older patients had, so help from a carer or visit by a district nurse was necessary. In addition, sharps and needles had to be disposed of properly.

Bayer submitted that vitamin K antagonists had a number of limitations including a narrow therapeutic index which required monitoring of the international normalised ratio (INR) and adjustment of the dose accordingly. There were three tablet strengths (1mg, 3mg, 5mg) which had to be used in various combinations in order to administer the required dose. This could be a source of dose error as noted in the Rapid Response Report (NPSA/2010/RRR018), 'Preventing fatalities from medication loading doses'. The report 'Medication involved in reported incidents' listed warfarin as the first of four critical medicines linked to loading dose errors.

Bayer stated that the dose of warfarin needed to be adjusted to take account of changes in food, drinks and concomitant medicines (warfarin summary of product characteristics (SPC)). Travelling and holidays might also be a concern and the majority of patients who had to attend clinics regularly for monitoring might find it difficult. Such considerations would have an impact on life style.

Bayer agreed with the complainant's comment that the use of all anticoagulants needed to be considered and monitored with care. Sections 4.4 and 5.1 of the Xarelto SPCs stated that 'There is no need for the monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests'. This was in marked contrast to warfarin which required regular monitoring of a patient's INR as part of the clinical routine.

Bayer submitted that the recommended dose for prevention of stroke and systemic embolism was 20mg once a day which was also the recommended maximum dose. Although the initial treatment of deep vein thrombosis (DVT) was 15mg twice a day for three weeks thereafter the dose was 20mg once a day. Bayer maintained that once a day dosing which did not need adjusting in patients, other than those with moderate to severe renal impairment, was simple. Simple did not imply that there was no risk of adverse events. However, it might be that once a day dosing, without the need for dose adjustment in the vast majority of patients, was more likely to result in patients being appropriately anticoagulated compared with warfarin. Bayer noted that even patients optimally treated with warfarin would only have an INR of 2-3 for approximately 60-70% of the time.

Bayer submitted that there were fewer interactions for Xarelto than warfarin with other medicines, food and drink.

Bayer stated that the advertisement made it clear that the indications for which Xarelto was to be used were DVT treatment and stroke prevention in AF which was consistent with the SPC. Furthermore, prominence was given to the indications for Xarelto recommended by NICE.

In addition to the above, Bayer also noted that the Atrial Fibrillation Association (patient organisation), the European Society of Cardiology (ESC) and clinicians with an interest in anticoagulation considered that the class of medicine to which Xarelto belonged was easier to manage, offered convenience and was simple.

Bayer noted that the Atrial Fibrillation Association's patient booklet, published in 2008 for individuals affected by atrial fibrillation and endorsed by the Department of Health, stated that 'Warfarin remains a popular and very effective drug at reducing the risk of stroke in high risk patients with atrial fibrillation. However, these new options offer some advantages. They do not need regular blood monitoring, they are more stable, having far fewer interactions with food, drinks and medications than warfarin and so [sic] easier to manage, the new oral anticoagulants are affective [sic] almost immediately after taking, and large clinical trials have shown them to be as effective as warfarin in reducing the risk of stroke'.

The 2012 focused update of the ESC Guidelines for the management of atrial fibrillation included the following key point 'The NOACs offer better efficacy, safety, and convenience compared with [oral anticoagulation] with [vitamin K antagonists]. Thus, where an oral anticoagulant is recommended, one of the NOACs – either a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (eg rivaroxaban, apixaban) – should be considered instead of adjusted-dose vitamin K antagonist (INR 2–3) for most patients with AF'.

Bayer quoted the following from published literature:

- Mousa (2010).

  'Rivaroxaban represents a potentially attractive alternative to warfarin, as it could enable simplified once-daily dosing, requires no therapeutic monitoring, and has a lower potential for drug interactions.'

- Buller (2010).

  'New oral anticoagulants hold the promise of simple fixed-dose regimens without the need for monitoring and could make extended use more attractive.'

- Ru San *et al* (2012).

  'With convenient fixed-dose administration, the NOACs facilitate anticoagulant management in AF in the community, which has hitherto been grossly underutilised. Guidelines should evolve towards simplicity in anticipation of greater use of NOACs among primary care physicians.'

- Buller and Darius (2010).

  'Against a background of prolonging anticoagulant treatment for many months to years, this study indicates that oral rivaroxaban, 15mg twice-daily for 3 weeks followed by 20mg once-daily, could provide clinicians and patients with a simple, single-drug approach for the acute and continued treatment of DVT that potentially improves the benefit-risk profile of anticoagulation.'

- Bauersachs *et al* (2010).

  'Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation.'

- Bauer (2011).

  'Rivaroxaban offers a simple and convenient single-drug oral approach to the initial treatment of venous thrombosis; this approach is also being tested with apixaban.'

- Cohen and Dobromirski (2012).

  'Moreover, the simple, once-daily oral administration of rivaroxaban could potentially improve adherence to extended-duration VTE treatment compared with the current standard of care in individuals with confirmed DVT or PE [pulmonary embolism].'

- Turpie (2012).

  'This article provides an overview of the phase III clinical development programmes for these novel OACs, with special focus on rivaroxaban. With encouraging data already emerging, the promise of a simplified single-drug approach for VTE treatment is on the horizon.'

- Mills *et al* (2012).

  'Initiating rivaroxaban approximately 12 or 24 hours after the last LMWH [low molecular weight heparin] dose (as appropriate) provides simple, well-tolerated transition strategy for thromboprophylaxis in patients undergoing THR [total hip replacement]/TKR [total knee replacement] surgery.'

- Bates and Weitz (2008).

  'Its rapid onset of action appears to eliminate the need for initial overlap with a parenteral anticoagulant like low-molecular-weight heparin, whereas its rapid offset of action should simplify management in the case of hemorrhage or the need for intervention.'

- Tagarakis *et al* (2010).

  'Many researchers have until now united their efforts in the endeavour to discover new anticoagulants, which would be simpler to use and safer to administer, so that patients would avoid both thromboembolic events as well as life threatening episodes of bleeding. One of these agents, that is hereby presented along with patents, is dabigatran, which promises much for the future, despite the fact that time and the awaited results of ongoing trials will be necessary for its establishment as a first-line anticoagulant. More specifically, based on the major trials of RELY and RECOVER, we could state that dabigatran has presented satisfactory outcomes in terms of bleeding and prevention of venous thromboembolism.'

In conclusion Bayer contended that Xarelto was simple and that this view was an accurate, fair, objective and unambiguous reflection of the literature. Consequently, Bayer considered that the advertisement at issue did not breach of Clauses 2, 3.2, 7.2, 7.9 or 9.1 of the Code.

PANEL RULING

The Panel noted the advertisement stated 'Xarelto for stroke prevention in AF, one tablet, once daily, simple'. It was clear that the reference to simple was in relation to the indication for stroke prevention in AF. It was also clear that 'simple' referred to the dosing regimen, as it appeared in the phrase 'one tablet, once daily, simple'. It was not a claim that generally Xarelto was simple to use.

The Panel agreed that the use of anticoagulants was complex. It considered that readers of the advertisement (GPs and health professionals working in primary care) would be aware of the complexities associated with the use of warfarin. It noted Bayer's submission regarding the need to monitor and adjust the doses of warfarin. Sections 4.4 and 5.1 of the Xarelto 20mg SPC stated that there was no need for the monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated, rivaroxaban levels could be measured by certain tests. Section 4.4 of the SPC stated that 'Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period'. The Panel noted the recommended dose of Xarelto in the prevention of stroke and systemic embolism in patients with AF and certain risk factors was 20mg per day. Therapy was to be continued long-term

provided the benefit of prevention of stroke and systemic embolism outweighed the risk of bleeding. Dose adjustment was needed in patients with renal impairment.

The Panel did not consider there was a general claim that Xarelto was simple to use as alleged. 'Simple' was used to describe the dosing regimen. The dosing regimen for Xarelto was not as complicated as for other products in this therapeutic area and in this context the broad indication of one tablet once a day for a number of patient populations might be viewed as simple.

The Panel did not consider that the claim 'one tablet, once daily, simple' was inconsistent with the SPC and thus ruled no breach of Clause 3.2. Nor was the claim an inaccurate reflection of the risks of using anticoagulants as alleged. No breach of Clauses 7.2 and 7.9 was ruled.

Given its rulings above the Panel did not consider the company had failed to maintain high standards nor had it brought discredit to or reduced confidence in the pharmaceutical industry. No breach of Clauses 9.1 and 2 was ruled.

Complaint received **29 October 2012**

Case completed **28 November 2012**