CASE AUTH/3035/4/18

ANONYMOUS HEALTH PROFESSIONAL v BAYER

Promotion of Xarelto

An anonymous complainant who described him/herself as a 'concerned UK health professional' complained about an Xarelto (rivaroxaban) advertisement by Bayer. Xarelto was a novel oral anticoagulant (NOAC) licensed to prevent thrombotic events in differing groups of patients. The advertisement at issue was headed 'Xarelto Protects Your High-Risk NVAF [non-valvular atrial fibrillation] Patients with Confidence'; the second of three bullet points below read 'In your patients with renal impairment'.

The complainant submitted that renally impaired patients were difficult to treat and in that regard, the Xarelto summary of product characteristics (SPC) stated:

> **'Limited clinical data for patients with severe renal impairment (creatinine clearance 15-29 ml/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 <15 ml/min.'**

In the complainant's view there was a big difference between using something with confidence and there being limited data and using it with caution or its use not being recommended. The complainant accepted that although this was technically within the licence, patients could still be put at risk.

The detailed response from Bayer is given below.

The Panel noted that the Xarelto SPC stated that limited data for patients with severe renal impairment indicated that rivaroxaban plasma concentration levels were significantly increased and so because of the possible increased risk of bleeding, Xarelto was to be used with caution in these patients. Use was not recommended in those with creatinine clearance CrCl of <15ml/min. In patients with moderate (CrCl 30-49ml/min) or severe (CrCl 15-29ml/min) renal impairment a reduced dose of Xarelto was recommended in patients with non-valvular atrial fibrillation.

The Panel queried Bayer's submission that 'renal impairment' was used in good faith to account for the majority of such patients who presented to a treating physician ie those with mild-to-moderate renal impairment and that a further detailed explanation about the severity of renal impairment and Xarelto dosing was addressed in the explanatory footnote. The Panel noted its comments above with regard to the reduced dose required in patients with moderate renal impairment and that rivaroxaban plasma levels might increase in these patients which could potentially lead to an increased bleeding risk. The Panel did not consider that the statement 'A single consideration for dose reduction (moderate and severe renal impairment, CrCl 15-49mL/min. CrCl 15-29mL/min: to be used with caution)' which appeared in very small font above the prescribing information as a footnote to the third bullet point 'With the simplest dosing algorithm of any NOAC' negated the otherwise misleading impression of the claim at issue in relation to renal impairment.

The Panel disagreed with Bayer's submission that the complainant's concerns were unfounded because 'confidence' in the claim 'Xarelto Protects Your High-Risk NVAF Patients with Confidence' referred to efficacy in preventing stroke, which was the possible consequence of NVAF. The Panel did not consider that this was clear, the indication was not stated in the body of the advertisement.

In the Panel's view the claim 'In your patients with renal impairment' was ambiguous as acknowledged by Bayer; the unqualified claim, read in conjunction with the prominent headline 'Xarelto Protects your High-Risk NVAF Patients with Confidence', implied that Xarelto could be used with confidence in all NVAF patients with renal impairment which was not so. The Panel considered that the misleading implication was compounded by the claim 'Tested in more high-risk patients than any other NOAC and prescribed to over 33 million patients across 7 indications'. The Panel considered that the claim was misleading and was not capable of substantiation and breaches of the Code were ruled. In the Panel's view Bayer had failed to maintain high standards and a breach of the Code was ruled.

The Panel considered that the claim at issue could potentially put the safety of NVAF patients with severe renal impairment (CrCl 15-29ml/min) and those with CrCl <15ml/min at risk and thus brought discredit upon and reduced confidence in the pharmaceutical industry, a breach of Clause 2 of the Code was ruled.

An anonymous complainant who described him/herself as a 'concerned UK health professional', complained about a Xarelto (rivaroxban) advertisement (ref UKXAR01180037d) placed by Bayer Plc in Pulse, April 2018. Xarelto was a novel, oral anticoagulant (NOAC) licensed to prevent thrombotic events in a number of different patient groups. The advertisement at issue had the headline 'Xarelto Protects Your High-Risk NVAF [non-valvular atrial fibrillation] Patients with Confidence'; the second of three bullett points below read 'In your patients with renal impairment'.

COMPLAINT

The complainant noted the bullet point 'In your patients with renal impairment' and submitted that such patients were difficult to treat and in that regard, he/she noted that the Xarelto summary of product characteristics (SPC) stated:

> 'Limited clinical data for patients with severe renal impairment (creatinine clearance 15-29 ml/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 <15 ml/min.'

The complainant stated that in his/her view there was a great difference between using something with confidence and there being limited data and use with caution/use was not recommended. The complainant accepted that this was technically within the licence but he/she still considered that it could put patients at risk.

When writing to Bayer the Authority asked it to consider the requirements of Clauses 2, 7.2, 7.4, 7.9 and 9.1 of the Code.

RESPONSE

Bayer noted that the complainant was concerned about the claim 'Xarelto Protects Your High-Risk NVAF Patients with Confidence […] in your patients with renal impairment'. Specifically, the complainant's concern appeared to be about the interpretation of confidence in NVAF patients with severe renal impairment (creatinine clearance (CrCl) ≤29ml/min).

Within the context of NVAF, the licensed indication for Xarelto was:

> 'Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.'

And with regard to renally impaired patients, the SPC stated:

> 'Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/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 < 15 ml/min (see sections 4.4 and 5.2).
>
> In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/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 15 mg once daily (see section 5.2).'

Therefore, patients with mild renal impairment were treated at the normal dose of 20mg, patients with moderate renal impairment (CrCl 30-49mL/min) at the reduced dose of 15mg, and patients with severe renal failure (CrCl 15-29ml/min) might be treated with caution at the reduced dose of 15mg. Use was not recommended in patients with a CrCl <15ml/min. Bayer noted that the majority of patients with renal impairment had mild-to-moderate impairment (CrCl >30ml/min).

Bayer acknowledged the complainant's concerns in that renally impaired NVAF patients could be difficult to treat which was why that important patient cohort was included in the pivotal Phase III study for Xarelto, as well as being in focus in the advertisement.

Bayer submitted, however, that the complainant's concerns were unfounded, as the 'confidence' referred to efficacy in preventing stroke, which was the possible consequence of NVAF in the claim 'Xarelto Protects Your High-Risk NVAF Patients with Confidence'. Additionally, the advertisement contained the following explanatory statement 'A single consideration for dose reduction (moderate and severe renal impairment, CrCl 15-49mL/min. CrCl 15-29mL/min: to be used with caution).' Consequently, Bayer did not agree that the advertisement placed patients at risk.
Bayer submitted that the mention of renal impairment was highly relevant to efficacy claims in high-risk NVAF because:

- the prevalence of both atrial fibrillation (AF) and renal impairment increased with age
- both conditions shared major risk factors, common comorbidities and polypharmacy
- irrespective of geographic location, observational studies revealed that older patients with AF and those with renal dysfunction were undertreated with anticoagulants (Fox *et al* 2011)
- both AF and renal impairment independently increased the risk of stroke and systemic thromboembolism (Olesen *et al* 2012, Fox *et al*)
- AF was known to increase the risk of stroke by a factor of approximately five
- renal impairment had also been shown to increase the risk of stroke or systemic embolism cumulatively in patients with AF (Olesen *et al*)
- In a registry of 132,372 patients with AF, non–end-stage chronic kidney disease increased the risk of stroke or systemic thromboembolism compared with no renal disease (hazard ratio, 1.49; 95% confidence interval [CI], 1.38 to 1.59; p<0.001) as did those requiring renal-replacement therapy (hazard ratio, 1.83; 95% CI, 1.57 to 2.14; p<0.001) (Olesen *et al*).

Bayer stated that the efficacy for Xarelto in patients with NVAF and renal impairment was substantiated by the following:

- in ROCKET AF (the pivotal Phase III study for Xarelto in NVAF), patients with mild renal

impairment (CrCl 50-80ml/min), and moderate renal impairment (CrCl 30-49ml/min) were included per protocol (Fox *et al*). Out of all the Phase III NOAC studies, ROCKET AF had the greatest proportion of high risk patients both in terms of stroke risk and bleeding risk

- patients with moderate renal impairment comprised 20.7% of the ROCKET AF study population (n=2950) (Fox *et al*). These patients with moderate renal impairment were administered a reduced dose of rivaroxaban (15mg once a day). ROCKET AF was the only Phase III NOAC study to have prospectively tested a specific renal dose
- 26.3% of the final analysis population in ROCKET AF had worsening renal function (WRF), defined as a decrease of >20% in CrCl from the screening CrCl measurement at any time during the study period. A number of these patients would have progressed to severe renal impairment during the course of the study. WRF patients who were randomized to receive rivaroxaban had a reduction in stroke or systemic embolism compared with those who took warfarin (1.54 vs 3.25 events per 100 patient-years) that was not seen in patients with stable renal function who were randomized to receive rivaroxaban (p=0.050). There was no difference in major or non-major clinically relevant bleeding among WRF patients randomized to warfarin vs rivaroxaban. (Fordyce *et al* 2016)
- The efficacy and safety (bleeding) results from ROCKET AF subjects with mild-to-moderate renal insufficiency behaved homogenously with the study population overall. Specifically, the reduced dose of rivaroxaban preserved the treatment effect of warfarin without increasing bleeding and with fewer fatal bleeds than warfarin (Fox *et al*).

Consequently, Xarelto was licensed for use in patients with mild, moderate and severe (CrCl>15ml/min) renal impairment, as well as in those with normal renal function. 'Confidence' in the advertisement pertained not only to the quality and quantity of data in high risk patients, but to the consistent safety and efficacy profile seen in these patients, including those with mild- to-moderate renal impairment, treated with rivaroxaban in the ROCKET AF study.

As with many disease areas or organ dysfunctions, renal impairment existed on a spectrum of severity and pathology, from the mildest, through to moderate then severe, or more granularly classified as Stage 1-5 renal impairment. It was generally well understood by clinicians that disease or pathophysiological processes such as renal impairment, were a spectrum, and that 'renal impairment' did not describe, on an individual patient basis, the full clinical spectrum of the condition to which they referred, and that there was more clinical granularity beyond this. 'Renal impairment' was used in good faith in the advertisement to account for the majority of such patients who presented to a treating physician ie those with mild-to-moderate renal impairment. Further detailed explanation about the severity of renal impairment and Xarelto dosing was addressed in the explanatory statement. In addition, other than the inclusion of the prescribing information, the main body of the advertisement contained no information about the posology or method of administration on which to make a prescribing decision. Bayer thus did not agree with the complainant's assertion that the advertisement could put patients at risk.

Bayer denied breaches of Clauses 2, 9.1, 7.4 and 7.9.

Bayer acknowledged, however, after careful consideration of the complaint, that there was the possibility for ambiguity in the claim in question. The wording of the advertisement could be further optimised and clarified in future, through the addition of a specific description of the classification of renally impaired patients included within the efficacy claim. Bayer thus accepted a breach of Clause 7.2. The advertisement, and all materials with related claims, had been withdrawn. Bayer submitted that it had amended relevant materials for future advertising.

PANEL RULING

The Panel noted that the advertisement in question had the headline 'Xarelto Protects Your High-Risk NVAF Patients with Confidence' followed by three bullet points: 'With a well-established efficacy and safety profile; In your patients with renal impairment' and 'With the simplest dosing algorithm of any NOAC'. Below these bullet points it stated 'Tested in more high-risk patients than any other NOAC and prescribed to over 33 million patients, across 7 indications'.

The Panel noted that Section 4.2 of the Xarelto 20mg SPC Special populations, Renal Impairment, stated that limited data for patients with severe renal impairment indicated that rivaroxaban plasma concentration levels were significantly increased. Therefore, Xarelto was to be used with caution in these patients. Use was not recommended in patients with CrCl in <15ml/min. In patients with moderate (CrCl 30-49ml/min) or severe (CrCl 15-29ml/min) renal impairment the reduced dose of 15mg once daily was recommended for the prevention of stroke and systemic embolism in patients with NVAF.

The Panel noted that Section 4.4 of the Xarelto 20mg SPC stated that in patients with severe renal impairment (CrCl <30ml/min) rivaroxaban plasma levels might be significantly increased (1.6 fold on average) which might lead to an increased bleeding risk. Xarelto was to be used with caution in patients with creatinine clearance 15-29ml/min. Use was not recommended in patients with CrCl <15ml/min.

Section 5.2 stated that there was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (CrCl 50-80ml/min), moderate (CrCl 30-49ml/min) and severe (CrCl 15-29ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced.

In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There were no data in patients with CrCl <15ml/min.

The Panel queried Bayer's submission that 'renal impairment' was used in good faith in the advertisement to account for the majority of such patients who presented to a treating physician ie those with mild-to-moderate renal impairment and that a further detailed explanation about the severity of renal impairment and Xarelto dosing was addressed in the explanatory footnote. The Panel noted its comments above with regard to the reduced dose required in patients with moderate renal impairment and that rivaroxaban plasma levels might increase (1.5 fold on average) in these patients which could potentially lead to an increased bleeding risk. The Panel did not consider that the statement 'A single consideration for dose reduction (moderate and severe renal impairment, CrCl 15-49mL/min. CrCl 15-29mL/min: to be used with caution)' which appeared in very small font above the prescribing information as a footnote to the bullet point 'With the simplest dosing algorithm of any NOAC' negated the otherwise misleading impression of the claim at issue in relation to renal impairment.

The Panel disagreed with Bayer's submission that the complainant's concerns were unfounded, as 'confidence' in the claim 'Xarelto Protects Your High-Risk NVAF Patients with Confidence' referred to efficacy in preventing stroke, which was the possible consequence of NVAF. The Panel did not consider that this was clear, the indication was not stated in the body of the advertisement.

In the Panel's view the claim 'In your patients with renal impairment' was ambiguous as acknowledged by Bayer and as a standalone claim it did not make grammatical sense. In the Panel's view the unqualified claim would be read in conjunction with the prominent headline claim 'Xarelto Protects your High-Risk NVAF Patients with Confidence' and implied that Xarelto could be used with confidence in all NVAF patients with renal impairment which was not so. The Panel considered that the misleading implication was compounded by the claim 'Tested in more high-risk patients than any other NOAC and prescribed to over 33 million patients across 7 indications'.

The Panel considered that the claim was misleading and was not capable of substantiation and a breach of Clauses 7.2 and 7.4 were ruled.

The Panel noted that Clause 7.9 was raised by the case preparation manager. Clause 7.9 stated that information and claims about adverse reactions must reflect available evidence or be capable of substantiation by clinical experience and it must not be stated that a product has no adverse reactions, toxic hazards or risks of addiction or dependency. The word 'safe' must not be used without qualification. The Panel did not consider that there was an allegation in this regard and therefore made no ruling.

The Panel noted its comments and rulings above and considered that Bayer had failed to maintain high standards and a breach of Clause 9.1 was ruled. The Panel noted Bayer's submission that the wording of the advertisement could be further optimised and clarified in future, through the addition of a specific description of the classification of renally impaired patients included within the efficacy claim. The advertisement, and all materials with related claims, had been withdrawn. Nonetheless, the Panel noted that examples of activities that were likely to be in breach of Clause 2 included prejudicing patient safety. The Panel noted the relevant sections of the SPC referred to above and the correlation between decrease in renal function and increase in rivaroxaban exposure, which might lead to an increased bleeding risk in some NVAF patients with renal impairment. The Panel considered that the claim at issue could potentially put the safety of NVAF patients with severe renal impairment (creatinine clearance 15-29ml/min) and those with CrCl <15ml/min at risk and thus brought discredit upon and reduced confidence in the pharmaceutical industry and a breach of Clause 2 was ruled.

Complaint received **26 April 2018**

Case completed **8 October 2018**