CASE AUTH/2791/9/15

ANONYMOUS, NON-CONTACTABLE v BAYER

Promotion of Xarelto

An anonymous, non-contactable complainant complained about the promotion of Xarelto (rivaroxaban) by Bayer plc. The material at issue was a leavepiece entitled 'Think NOACs [novel oral anticoagulants] and Renal Impairment in Non-Valvular AF [atrial fibrillation]. Think Xarelto'.

Xarelto was indicated for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation (AF) with one or more risk factors, such as congestive heart failure (CHF), hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

The complainant drew attention to a table which compared Xarelto and two other NOACs; apixaban (Eliquis, Bristol-Myers Squibb) and dabigatran (Pradaxa, Boehringer Ingelheim), when there had been no head-to-head trials. The complainant stated that the footer tried to justify this but it was small and easily missed. In his/her view the data should not be displayed that way but if so, it should be very clear what each trial comprised.

The detailed response from Bayer is given below.

The Panel noted that no explanation was given and so in the Panel's view it was not immediately clear that the table presented the demography of the three studies and was not a comparison of safety or efficacy as submitted by Bayer. The Panel considered that the page was ambiguous as the comparative claim juxtaposed to the table 'Xarelto: Proven safety profile and efficacy in a higher-risk non-valvular AF patient population than any other NOAC' referenced to the three studies included within the table appeared to refer to the comparative data shown in the table. This was not so. Some readers might reasonably assume that there had been direct clinical comparisons of the safety profile and efficacy of Xarelto, Eliquis and Pradaxa which was not so. It appeared that the complainant might have been so misled. The footnote 'These trials were conducted with different designs and evaluated different populations, so direct comparisons of their results cannot be made' below the table was not sufficiently prominent or sufficiently clear to qualify the misleading impression. The footnote appeared to be inconsistent with Bayer's submission that the table presented demography not results. In addition, the Panel considered the page was such that on the balance of probabilities, some readers would assume that direct clinical comparisons of the three medicines' safety profile and efficacy in higher risk non-valvular AF-patient population had occurred which was not so.

The Panel considered that the table was misleading as alleged. Breaches of the Code were ruled.

An anonymous, non-contactable complainant complained about the promotion of Xarelto (rivaroxaban) by Bayer plc. The material at issue was a leavepiece (ref L.GB.12.2014.9153a) entitled 'Think NOACs [novel oral anticoagulants] and Renal Impairment in Non-Valvular AF [atrial fibrillation]. Think Xarelto'. The leavepiece stated that Xarelto was the only National Institute for Health and Clinical Excellence (NICE) approved NOAC with a prospectively tested renal dose (15mg once daily). The leavepiece was for the sales force to use with health professionals.

Xarelto was indicated for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation (AF) with one or more risk factors, such as congestive heart failure (CHF), hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

COMPLAINT

The complainant drew attention to a table which compared three NOACs; rivaroxaban (Xarelto), apixaban (Eliquis, Bristol-Myers Squibb) and dabigatran (Pradaxa, Boehringer Ingelheim), when there had been no head-to-head trials. The footer tried to justify this but it was small and easily missed. The complainant did not consider that the data should be displayed that way but if so, it should also be very clear what each trial comprised.

When writing to Bayer, the Authority asked it to respond in relation to Clauses 7.2 and 7.3 of the Code.

RESPONSE

Bayer submitted that the presentation, format and content of the comparative table on page 5 were such that it did not mislead.

Bayer explained that ROCKET AF was a randomised double-blind, double dummy event-driven trial with an objective to demonstrate non-inferiority of rivaroxaban compared with warfarin in patients (n=14,264) with non-valvular atrial fibrillation who had a history of stroke or at least two additional independent risk factors for stroke. The primary efficacy endpoint was the composite of stroke and non-central nervous system (CNS) systemic embolism and the primary safety endpoint was the composite of major and clinically-relevant non-major bleeding. Patients were randomly assigned to receive either fixed dose rivaroxaban (20mg daily or 15mg daily in patients with a creatinine clearance of 30-49ml/min) or adjusted dose warfarin. Furthermore, with regard to renal impairment, the Xarelto summary of product characteristics (SPC) stated that:

'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 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 15mg once daily.'

With respect to the table at issue, Bayer stated that the CHADS2 scores (used to estimate stroke risk in patients with AF) for each anticoagulant were presented in three columns which were differentiated by colour and titles which specified the trial from which the data for each NOAC was derived. Furthermore, the trial title was in large upper case font. Bayer submitted that the differentiators for each column made it very clear that the data was derived from three different, separate trials and that there was nothing to suggest or imply that the trials were direct 'head-to-head' comparisons. This was reinforced by a footnote which emphasized that 'These trials were conducted with different designs and evaluated different populations so direct comparisons of their results cannot be made'.

Bayer submitted that the font size and contrast between the colour of the font and the background colour was such that it was not easily missed. The clarity of the footnote was such that its prominence was at least equivalent to that which was ordinarily seen in promotional and other materials designed for health professionals. Bayer noted that the table presented demography and was not a comparison of safety or efficacy.

Bayer stated that the table in question highlighted the mean CHADS2 score in all three relevant trials (ROCKET AF (Xarelto), ARISTOTLE (apixaban) and RE-LY (dabigatran)) and the percentage of patients in each sub-group that contributed to that score. The total number of patients in all three trials was also shown for comparison. The table therefore highlighted the higher risk non-valvular AF patient population according to the CHADS2 criteria in the ROCKET AF trial compared with ARISTOTLE and RE-LY.

Bayer noted that reference was also made to the fact that factors contributing to a higher risk of stroke might also contribute to renal impairment with the caveats of when and where Xarelto was licensed in this group of patients. The information was fully referenced in the material.

Bayer submitted that as per the SPC and clinical trial data the leavepiece made it clear that the Xarelto 15mg dose was intended for patients with non-valvular AF and for the appropriate severity of renal impairment.

Bayer therefore submitted that neither the table nor any of the accompanying information was misleading in breach of Clause 7.2. Furthermore, sufficient information was provided for the reader, so as not to mislead, however all three trials and the data shown were also clearly referenced if the reader wished to gain further information for each trial. Bayer also submitted that the principles of Clause 7.3 were maintained as the table compared medicines intended for the same purpose and no confusion was created between Bayer's or the competitor medicines.

PANEL RULING

The Panel noted the complainant was anonymous and non-contactable. As stated in the introduction to the Constitution and Procedure such complaints were accepted and like all complaints, judged on the evidence provided by both parties. Complainants had the burden of proving their complaint on the balance of probabilities.

The Panel noted the allegation that the table in question was misleading as it compared three NOACs despite there being no head-to-head studies and the company's footnote could easily be missed due to its small font size.

The Panel noted that direct head-to-head studies were not necessarily needed to substantiate a comparison of products provided that such a comparison was not misleading and complied with the Code.

The Panel noted that page 5 of the leavepiece was headed 'Factors contributing to higher risk of stroke may also contribute to renal impairment'. Below the heading and directly above the table in question was the prominent claim 'Xarelto: Proven safety profile and efficacy in a higher risk non-valvular AF-patient population than any other NOAC'. The references to this claim included three studies; Patel et al, Granger et al and Connolly et al (Rocket AF, ARISTOTLE and RE-LY), which were compared in the table. The other three references cited related to ROCKET AF.

The Panel noted that the table in question featured the mean CHADS2 score and what appeared to be each of its five components (CHF, hypertension, ≥ 75 years old, diabetes and prior stroke or TIA) for all three trials (ROCKET AF (Xarelto), ARISTOTLE (apixaban) and RE-LY (dabigatran)). The percentage of patients in each component that contributed to that score was given. The figures for Xarelto were higher than the figures for apixaban and dabigatran.

The Panel noted Bayer's submission that the table was not a comparison of safety or efficacy and it highlighted the higher risk non-valvular AF patient population according to the CHADS2 criteria in the ROCKET AF trial compared with ARISTOTLE and RE-LY.

The Panel noted that no background information or explanation was given and so in the Panel's view it was not immediately clear that the table presented the demography of the three studies and was not a comparison of safety or efficacy as submitted

by Bayer. The Panel considered that the page was ambiguous as the comparative claim juxtaposed to the table 'Xarelto: Proven safety profile and efficacy in a higher-risk non-valvular AF patient population than any other NOAC' referenced to the three studies included within the table appeared to refer to, or be based on or substantiated by, the comparative data shown in the table. This was not so. Some readers might reasonably assume that there had been direct clinical comparisons of the safety profile and efficacy of Xarelto, Eliquis and Pradaxa which was not so. It appeared that the complainant might have been so misled. The Panel noted that the footnote 'These trials were conducted with different designs and evaluated different populations, so direct comparisons of their results cannot be made' which appeared in small typeface below the table was not sufficiently prominent or sufficiently clear to qualify the misleading impression of the page. The footnote appeared to be inconsistent with Bayer's submission that the table presented demography not results. In addition, the Panel considered the page was such that on the balance of probabilities, some readers would assume that direct clinical comparisons of the three medicines' safety profile and efficacy in higher risk non-valvular AF-patient population had occurred which was not so.

The Panel considered that the table was misleading as alleged. Breaches of Clauses 7.2 and 7.3 were ruled.

Complaint received **3 September 2015**

Case completed **16 October 2015**