BRISTOL-MYERS SQUIBB and PFIZER/DIRECTOR v BAYER

Alleged breach of undertaking

Bristol-Myers Squibb and Pfizer complained that a Xarelto (rivaroxaban) leavepiece entitled 'For elderly patients taking aspirin for stroke prevention ... It's time to rethink their protection' breached the undertaking given by Bayer in Case AUTH/2650/11/13.

As the complaint was about an alleged breach of undertaking it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

The complainants referred to Case AUTH/2650/11/13 which concerned another Xarelto leavepiece and noted the Panel's view that 'although Patel *et al* [2011, the ROCKET AF trial] had shown that overall Xarelto had a comparable safety profile compared with warfarin, it was important for health professionals to know that patients treated with Xarelto were at increased risk of GI [gastrointestinal] bleeds vs patients on warfarin; the health professionals could thus manage that risk appropriately'. Bayer was ruled in breach of the Code.

The leavepiece now at issue profiled a patient, a 75 year old woman with non-valvular atrial fibrillation (NVAF) who was currently prescribed aspirin. The material thus unequivocally focussed on the indication of stroke prevention in NVAF.

Bristol-Myers Squibb and Pfizer noted that a page headed 'Xarelto: Demonstrated safety profile across indications' provided the following information about the safety of Xarelto in NVAF:

> **'In patients with non-valvular AF, from the ROCKET-AF trial:**
> - **Xarelto demonstrated a comparable safety profile vs warfarin.'**

Bristol-Myers Squibb and Pfizer stated that following this text there was no further mention of safety information from Patel *et al* (2011). The remainder of the page highlighted bleeding safety data from EINSTEIN which was data from a population with venous thromboembolism (VTE) not NVAF. Importantly, no secondary safety endpoints for bleeding from Patel *et al* had been included. GI bleeding rates for Xarelto compared with warfarin from Patel *et al* had been omitted.

The complainants alleged that the page was misleading as not all key safety endpoints for Xarelto were comparable to warfarin in Patel *et al*. Bristol-Myers Squibb and Pfizer noted that major bleeding from GI sites occurred significantly more frequently in the rivaroxaban group than in the warfarin group; 224 bleeding events (3.2%) vs 154 bleeding events (2.2%) (p<0.001) respectively.

Furthermore Section 4.4 of the Xarelto summary of product characteristics (SPC) highlighted the difference between Xarelto and warfarin with regard to GI bleeding including:

> **'Haemorrhagic risk**
> **… In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anaemia were seen more frequently during long-term rivaroxaban treatment compared with VKA [vitamin K antagonist] treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/ haematocrit could be of value to detect occult bleeding, as judged to be appropriate.'**

Bristol-Myers Squibb and Pfizer alleged that Bayer had failed to comply with the undertaking in Case AUTH/2650/11/13 and was in breach of various clauses of the Code including Clause 2.

The detailed response from Bayer is given below.

The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted its rulings in Case AUTH/2650/11/13 related to a page headed 'A reassuring safety profile matters' and sub-headed 'Xarelto significantly reduces the risk of fatal bleeds by 50% vs warfarin in AF [atrial fibrillation]'. The page detailed safety data from Patel *et al* which compared Xarelto and warfarin. The page featured a bar chart above the claim 'Comparable safety profile vs warfarin with an increased risk of bleeding from GI sites'. The Panel noted that the increased risk of bleeding from GI sites had not been quantified in the same way as the decreased risk of other bleeding events had been in the bar chart (event rate, relative risk and p-values). In the Panel's view the failure to give readers the comparable data for GI bleeding was misleading and a breach had been ruled.

Turning to Case AUTH/2776/7/15, the Panel noted the page at issue was headed 'Because of Jean's age and hypertension she's at moderate risk of a major bleed' followed by 'Xarelto: Demonstrated safety profile across indications' above 'In patients with non-valvular AF, from the ROCKET-AF trial: Xarelto demonstrated a comparable safety profile vs warfarin'. The Panel noted that the claim 'Xarelto demonstrated a comparable safety profile vs warfarin' was referenced to Patel *et al*, rather than the ROCKET AF trial.

The Panel considered that there were differences between the material considered in Case

AUTH/2650/11/13 and that now at issue. The leavepiece at issue broadly compared the safety profile of Xarelto vs warfarin. The claim at issue did not mention specific bleeding sites or the risk of bleeds *per se*. Subsequent claims on the same page did not mention specific bleeding sites although the risk of major and non-major and clinically relevant bleeds were referred to. The material at issue in Case AUTH/2650/11/13 had, *inter alia*, compared certain bleeding events in a bar chart and referred in text below this bar chart to GI bleeding events. The Panel considered the claim now at issue 'In patients with non-valvular AF, from the ROCKET-AF trial: Xarelto demonstrated a comparable safety profile vs warfarin', was not sufficiently similar to that at issue in Case AUTH/2650/11/13 for it to be covered by the undertaking given in that case. Thus the Panel ruled no breach of the Code including Clause 2.

Bristol-Myers Squibb and Pfizer Limited complained, as the Bristol-Myers Squibb and Pfizer Alliance, that promotional material for Xarelto (rivaroxaban) breached the undertaking given by Bayer plc in Case AUTH/2650/11/13. Bristol-Myers Squibb and Pfizer were the complainants in that case.

As the complaint was about an alleged breach of undertaking it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

Bristol-Myers Squibb and Pfizer now drew attention to a six page, gate-folded leavepiece entitled 'For elderly patients taking aspirin for stroke prevention... It's time to rethink their protection' (reference January 2015 L.GB.12.2014.9154,). The leavepiece introduced a patient profile, Jean, a 75 year old woman with non-valvular atrial fibrillation (NVAF) who was currently prescribed aspirin.

The indications for Eliquis (apixaban) jointly marketed by Bristol-Myers Squibb and Pfizer and Xarelto included the prevention of stroke and systemic embolism in adults with NVAF with one or more risk factors such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

COMPLAINT

Bristol-Myers Squibb and Pfizer referred to Case AUTH/2650/11/13 which concerned a Xarelto leavepiece (reference L.GB.02.2013.1576c, February 2013). The complainants noted that in that case the Panel's view was 'although Patel *et al* [2011, ROCKET-AF trial] had shown that overall Xarelto had a comparable safety profile compared with warfarin, it was important for health professionals to know that patients treated with Xarelto were at increased risk of GI [gastrointestinal] bleeds vs patients on warfarin; the health professionals could thus manage that risk appropriately'. Bayer was ruled in breach of Clauses 7.2 and 9.1.

The complainants stated that in the leavepiece now at issue the patient profile, a woman with NVAF, was referred to on five of the six pages and thus the leavepiece unequivocally focussed on the indication of stroke prevention in NVAF.

Bristol-Myers Squibb and Pfizer drew attention to a page in the leavepiece which referred to the safety profile of Xarelto. The page was headed 'Xarelto: Demonstrated safety profile across indications'. The information provided about the safety of Xarelto in NVAF was:

> 'In patients with non-valvular AF, from the ROCKET-AF trial:
> - Xarelto demonstrated a comparable safety profile vs warfarin'

Bristol-Myers Squibb and Pfizer stated that following this text there was no further mention of safety information from Patel *et al* (2011). Importantly, no secondary safety endpoints for bleeding from Patel *et al* had been included in the material. GI bleeding rates for Xarelto compared with warfarin from Patel *et al* had been omitted.

Bristol-Myers Squibb and Pfizer alleged that the page was misleading as not all key safety endpoints for Xarelto were comparable to warfarin in Patel *et al*. Based on the published paper and supplementary appendix, Bristol-Myers Squibb and Pfizer noted that major bleeding from GI sites occurred significantly more frequently in the rivaroxaban group than in the warfarin group; 224 bleeding events (3.2%) vs 154 bleeding events (2.2%) ($p<0.001$) respectively.

Furthermore the Xarelto summary of product characteristics (SPC) (December 2014), in Section 4.4 Special Warnings and Precautions for use, contained the following text highlighting the difference between Xarelto and warfarin with regard to GI bleeding:

> <u>Haemorrhagic risk</u>
> '…In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anaemia were seen more frequently during long-term rivaroxaban treatment compared with VKA [vitamin K antagonist] treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.'

In summary Bristol-Myers Squibb and Pfizer alleged that Bayer had failed to comply with the undertaking in Case AUTH/2650/11/13. The current material omitted important safety information when informing health professionals about the GI bleeding profile of Xarelto for stroke prevention in NVAF compared with warfarin. Because of the seriousness of this matter the companies alleged breaches of Clauses 2, 7.2, 9.1 and 29.

RESPONSE

Bayer noted that the undertaking from Case AUTH/2650/11/13 related to the leavepiece, 'Anticoagulation: why Xarelto (rivaroxaban) matters', (ref L.GB.02.2013.1576c) and specifically to a bar chart on page 4, as well as the content under the bullet point 'safety profile matters' on page 8 of that leavepiece. The bar chart and bullet point detailed certain safety events from the ROCKET AF trial that were favourable to Xarelto (fatal bleeding,

intracranial bleeding and critical organ bleeding events). However, in the bar chart and on page 4, presentation of unfavourable GI bleeding data was not given equal prominence as the favourable events.

ROCKET AF was a randomised double-blind, double dummy event-driven trial with an objective to demonstrate non-inferiority of Xarelto compared with warfarin in patients with NVAF who had a history of stroke or at least two additional independent risk factors for stroke. 14,264 patients were randomized to either rivaroxaban or warfarin.

The primary efficacy endpoint was the composite of stroke and non-CNS systemic embolism. In the pre-specified per protocol population rivaroxaban was shown to be non-inferior to warfarin while demonstrating superior efficacy in the pre-specified safety as treated analysis.

The primary safety endpoint was the composite of major and clinically relevant non-major bleeding. Rates of major and non-major clinically relevant bleeding were similar in the Xarelto and warfarin groups. There were no differences between Xarelto and warfarin in the individual components of the composite primary safety endpoint. Rates of major bleeding were similar in the Xarelto and warfarin groups (3.6% and 3.4%, respectively; p=0.58). The rates of non-major clinically relevant bleeding were also similar in the Xarelto and warfarin groups (11.8 and 11.4% respectively; p=0.35).

Bayer noted that the present complaint (Case AUTH/2776/7/15) also related to a claim based on ROCKET AF data. The claim at issue was:

> 'In patients with non-valvular AF, from the ROCKET-AF trial:
> • Xarelto demonstrated a comparable safety profile versus warfarin'

Bayer did not agree that the claim failed to comply with the undertaking given in Case AUTH/2650/11/13 as alleged. In the current leavepiece only data relating to the primary safety endpoint was presented. Unlike the leavepiece at issue in Case AUTH/2650/11/13 there was no reference to specific bleeding events.

Bayer stated that in Case AUTH/2650/11/13 the Panel noted that

> '... below the bar chart there was a claim "Comparable safety profile vs warfarin with an increased risk of bleeding from GI [gastrointestinal] sites"'

and

> '... the increased risk of bleeding from GI sites had not been quantified in the same way as the decreased risk of other bleeding events had been in the bar chart (event rate, relative risk and p values). In the Panel's view the failure to give readers the comparable data for GI bleeding was misleading and a breach of Clause 7.2 was ruled.'

As a result of the Panel's ruling, Bayer submitted that it undertook to provide comparable data for GI bleeding whenever data for other bleeding events, where there was significant advantage for Xarelto vs warfarin, were presented and that the GI data would always be quantified in the same way.

Bayer stated that in the leavepiece now at issue there were no references to the aforementioned specific favourable bleeding events with Xarelto. Bayer therefore submitted that there had been no breach of undertaking.

Bayer noted that the leavepiece at issue in Case AUTH/2650/11/13 was withdrawn as was all material with a similar presentation of the favourable safety events in question that were not balanced by equal presentation of Xarelto GI bleeding data. In addition, a briefing was drafted and circulated to clarify this, and other undertakings from the case.

In response to a request for further information for specific comments on Clauses 7.2, 9.1, 29 and 2 with respect to the leavepiece now at issue, Bayer stated the complaint was about a breach of undertaking. More specifically, the allegation was that the material in question omitted important safety information when communicating with health professionals regarding the GI bleeding profile with rivaroxaban for stroke prevention in NVAF. The complainants concluded that because of the alleged breach of undertaking, the material was in breach of Clauses 7.2, 9.1, 29 and 2.

Bayer noted that the claim

> 'In patients with non-valvular AF, from the ROCKET-AF Trial
> • Xarelto demonstrated a comparable safety profile vs warfarin'

did not include the GI bleeding profile. Bayer submitted that the justification for this was that there was no reference to other specific bleeding events as already described previously. Bayer submitted that the undertaking from Case AUTH/2650/11/13 was that Bayer agreed to provide comparable data for GI bleeding whenever data for other bleeding events from the ROCKET AF trial (like intracranial haemorrhage retroperitoneal and fatal bleeding, where there were significant advantages for Xarelto vs warfarin) were presented, and that the GI bleeding data would always be presented in the same way.

Consequently Bayer did not accept that there had been a breach of undertaking and therefore of Clauses 29, 7.2, 9.1 or 2.

PANEL RULING

The Panel noted that Bristol-Myers Squibb and Pfizer alleged a breach of the undertaking given in Case AUTH/2650/11/13. The companies also referred to the omission of important safety information when communicating to health professionals regarding the GI bleeding profile of rivaroxaban for stroke prevention in NVAF compared to warfarin and stated that due to the seriousness of this matter the material was also in breach of Clauses 7.2, 9.1 and 2. The Panel

noted that the introductory paragraph to the complaint stated that it concerned a breach of undertaking. The Panel thus considered the complaint solely in relation to the alleged breach of undertaking and Clauses 2, 9.1 and 29.

The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that Pfizer and Bristol-Myers Squibb alleged that the claim 'In patients with non-valvular AF, from the ROCKET-AF trial: Xarelto demonstrated a comparable safety profile vs warfarin' in the leavepiece now at issue, January 2015 L.GB.12.2014.9154, was such that Bayer had failed to comply with the undertaking given in Case AUTH/2650/11/13.

The Panel noted its rulings in Case AUTH/2650/11/13 related to page 4 of a booklet headed 'A reassuring safety profile matters' and sub-headed 'Xarelto significantly reduces the risk of fatal bleeds by 50% vs warfarin in AF [atrial fibrillation]'. The page detailed safety data from Patel *et al* which compared Xarelto and warfarin. The principal safety endpoint in Patel *et al* was a composite of major and non-major clinically relevant bleeding events; such events occurred in 14.9% of Xarelto patients vs 14.5% of warfarin-treated patients (p=0.44). Rates of major bleeding were similar in the two groups (3.6% and 3.4% respectively, p=0.58) although major bleeding from GI sites occurred more frequently in the Xarelto group (3.2% vs 2.2%, p<0.001). The page at issue in Case AUTH/2650/11/13 featured a bar chart above the claim 'Comparable safety profile vs warfarin with an increased risk of bleeding from GI sites'. The Panel noted that the increased risk of bleeding from GI sites had not been quantified in the same way as the decreased risk of other bleeding events had been in the bar chart (event rate, relative risk and p-values). In the Panel's view the failure to give readers the comparable data for GI bleeding was misleading and a breach of Clause 7.2 had been ruled.

Turning to the present case, Case AUTH/2776/7/15, the Panel noted the leavepiece was entitled 'For elderly patients taking aspirin for stroke prevention…' with a picture of a middle aged lady on the front 'Jean' who at 75 had been diagnosed with NVAF one month ago. She had a prior medical history of hypertension and mild congestive heart failure.

The page at issue was headed 'Because of Jean's age and hypertension she's at moderate risk of a major bleed' followed by 'Xarelto: Demonstrated safety profile across indications' above 'In patients with non-valvular AF, from the ROCKET AF trial: Xarelto demonstrated a comparable safety profile vs warfarin'. The Panel noted that the claim 'Xarelto demonstrated a comparable safety profile vs warfarin' was referenced to Patel *et al*, rather than the ROCKET AF trial.

The Panel considered that there were differences between the material considered in Case AUTH/2650/11/13 and that now at issue. The Panel considered that the material now at issue broadly compared the safety profile of Xarelto vs warfarin. The claim at issue did not mention specific bleeding sites or the risk of bleeds *per se*. Neither did subsequent claims on the same page mention specific bleeding sites although the risk of major and non-major and clinically relevant bleeds were referred to. The material previously at issue in Case AUTH/2650/11/13 had, *inter alia*, compared certain bleeding events in a bar chart and referred in text below this bar chart to GI bleeding events. The Panel considered the claim in the leavepiece now at issue 'In patients with non-valvular AF, from the ROCKET-AF trial: Xarelto demonstrated a comparable safety profile vs warfarin', was not sufficiently similar to that at issue in Case AUTH/2650/11/13 for it to be covered by the undertaking given in that case. Thus the Panel ruled no breach of Clause 29. Given this ruling the Panel also ruled no breach of Clauses 2 and 9.1.

Complaint received **30 June 2015**

Case completed **19 August 2015**