CASE AUTH/2650/11/13

BRISTOL-MYERS SQUIBB and PFIZER v BAYER

Promotion of Xarelto

Bristol-Myers Squibb and Pfizer complained about a Xarelto (rivaroxaban) exhibition panel and promotional booklet used by Bayer at the Eurostroke Conference. Eliquis (apixaban) jointly marketed by Bristol-Myers Squibb and Pfizer and Xarelto were both anticoagulants indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

The detailed response from Bayer is given below.

The exhibition panel featured the claim at issue 'Xarelto … Highly Effective Protection From Day One' below the headline 'Efficacy matters:' and was followed by a bar chart which compared the efficacy of Xarelto with that of warfarin. Bristol-Myers Squibb and Pfizer alleged that the claim was exaggerated and could not be substantiated. Whilst Xarelto might exhibit some Factor Xa (FXa) inhibition on day one, 'protection' implied that strokes could be prevented on day one which could not be substantiated. Additionally 'highly effective' from day one was also exaggerated and could not be substantiated.

The Panel noted that the bar chart depicted the results of Patel *et al* (2011) and showed that Xarelto was non-inferior to warfarin for the primary endpoint of stroke or systemic embolism. The Panel noted Bayer's submission that the anticoagulant effect of Xarelto was due to its inhibition of FXa and that maximum inhibition (and Cmax) occurred within hours of dosing. Warfarin inhibited the synthesis of vitamin K dependent coagulation factors and although anticoagulation effects occurred within 24 hours, peak anticoagulation might be delayed 72 to 96 hours. The Panel acknowledged that inhibition of FXa would prevent clotting and thus protect patients from stroke and systemic embolism and in that regard, Xarelto exhibited maximum inhibition on day one. Nonetheless, efficacy of Xarelto was measured in terms of the prevention of stroke and systemic embolism – inhibition of FXa was not, in itself, a measure of efficacy. In the Panel's view, the claim at issue, under the heading 'Efficacy matters:' implied that on day one, Xarelto had a direct measurable effect on the prevention of stroke and systemic embolism. This was not so. The Panel considered that the claim was exaggerated and could not be substantiated and breaches of the Code were ruled.

With regard to the promotional booklet, Bristol-Myers Squibb and Pfizer submitted that, on page 4, only favourable secondary endpoints had been given prominence. It was not clear that the primary endpoint (stroke and systemic embolism) was non-inferior to warfarin. The primary safety analysis in Patel *et al*, 'major and non-major clinically relevant bleeding' and the safety endpoint, 'major bleeding', had not been included. Both of these endpoints showed no significant difference for Xarelto vs warfarin, and by omitting them clinicians were not presented with a fair and balanced overview of the safety analysis; Bristol-Myers Squibb and Pfizer alleged that Bayer had 'cherry picked' favourable data.

The complainants submitted that page 4 further stated that there were more gastrointestinal bleeds vs warfarin but there was no quantification of the increased risk or p-values to demonstrate that the increased risk was statistically significant.

Bristol-Myers Squibb and Pfizer were concerned about the claim on the same page, 'Even in your fragile patients, Xarelto has an established safety profile' and noted the restrictiveness in the Code with regard to the use of the word safe and grammatical derivations thereof. The statement regarding renally impaired patients (an example of 'fragile' patients) was inconsistent with the Xarelto summary of product characteristics (SPC) and underplayed the safety data. The elderly population was also highlighted as a potential 'fragile' patient population. However, in the elderly there was a high prevalence of renal impairment and so the above concerns highlighted for renal impairment also applied to a 'fragile' elderly population. To refer to an established safety profile in these 'fragile' patients was misleading and the safety claim could not be substantiated.

The Panel noted that the booklet, entitled 'Anticoagulation: why Xarelto matters', introduced the reader to Xarelto, its four licensed indications and that it was now widely prescribed. Page 4 was 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 the safety data from Patel *et al* which compared Xarelto and warfarin.

The Panel noted the allegation that page 4 did not refer to the primary [efficacy] endpoint (stroke and systemic embolism) or make it clear that this endpoint was non-inferior to warfarin. The Panel noted that page 4 dealt with safety issues of the two medicines and featured a bar chart which depicted bleeding events where there was a significant advantage for Xarelto vs warfarin. In that regard the Panel did not consider that the lack of efficacy data was misleading, particularly when that data showed Xarelto to be non-inferior to warfarin. In the Panel's view, health professionals would not be misled into prescribing a product which Bayer claimed to have a 'reassuring safety profile' but which was less efficacious than the competitor to which it was compared. No breach of the Code was ruled.

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'. The Panel noted that during inter-company dialogue Bayer had agreed to add the p-value to the claim in question and thus this matter was not considered by the Panel. The Panel noted however, 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 the Code was ruled.

In the Panel's view the claim, 'Even in your fragile patients, Xarelto has an established safety profile', did not imply that Xarelto was safe to use in fragile patients – it referred to the safety profile of the medicine and was not an absolute claim for safety. The Panel ruled no breach of the Code. The Panel considered that the claim could be substantiated and no breach of the Code was ruled. Given these two rulings, the Panel did not consider that Bayer had failed to maintain high standards and ruled accordingly.

The Panel noted that following the claim about fragile patients, those with moderate to severe renal impairment and the elderly (≥75 years) were listed as examples of such patients. The Panel noted that Xarelto could be prescribed to those with a creatinine clearance as low as 15ml/min (severe renal impairment) or more but was not recommended for patients with a creatinine clearance of <15ml/min (renal failure). The Panel further noted the reference to elderly patients as a separate group and that many of them would have some degree of renal impairment. Age alone, however, was not a reason to reduce the dose of Xarelto. As above, the Panel did not consider that the reference to an established safety profile in the elderly or those with moderate or severe renal impairment was a claim for absolute safety in either group. No breach of the Code was ruled. The Panel considered that the claim could be substantiated; no breach of the Code was ruled. The Panel did not consider that Bayer had failed to maintain high standards and ruled no breach of the Code.

Bristol-Myers Squibb and Pfizer alleged that page 5 underplayed the complexity of anticoagulation treatment for patients and clinicians, whereby stroke prevention had to be balanced against the risk of bleeding; the heading 'Simplicity matters' was an all-embracing, general claim and implied that using Xarelto was simple. Page 5 also included the claim 'Once-daily Xarelto provides fast-acting, 24 hour protection'. As described above, Bristol-Myers Squibb and Pfizer did not consider that it could be adequately substantiated and was an exaggerated claim.

The Panel noted that page 5 was headed 'Simplicity matters' and sub-headed in emboldened text, 'A once-daily novel oral anticoagulant that provides 24hr protection …'. The sub-heading continued further down the page with '… without the need to adjust dose for a patient's age, gender or body weight' which was similarly emboldened. There then followed a description of the dosage regimen; one 20mg tablet once-daily (with food) for patients with atrial fibrillation and one 15mg table once-daily (with food) for atrial fibrillation patients with moderate or severe renal impairment. The Panel noted that the heading 'Simplicity matters' was on a page which clearly dealt with the once-daily dosing regimen of Xarelto. The Panel considered that the intended audience (nurses, payors, pharmacists and physicians) would be well acquainted with the complexities of warfarin therapy; the dosing regimen and monitoring of Xarelto patients was not as complicated. In the Panel's view, health professionals would know that with any anticoagulant, the risk of unintended bleeding had to be balanced against stroke prevention. The Panel did not consider that 'Simplicity matters' underplayed the complexity of anticoagulant therapy as alleged. No breach of the Code was ruled. The Panel did not consider that Bayer had failed to maintain high standards and no breach of the Code was ruled .

With regard to the claim 'Once-daily Xarelto provides fast-acting, 24 hour protection', the Panel noted its comments above. The Panel considered that, contrary to Bayer's submission, the claim implied that Xarelto had been shown to have a fast and measurable effect on the prevention of stroke and systemic embolism. In the Panel's view this was not so. The Panel thus considered that the claim was exaggerated and could not be substantiated and breaches of the Code were ruled.

Bristol-Myers Squibb and Pfizer noted that the sub-heading to page 6 was, 'Once-daily dosing improves compliance …'. Bristol-Myers Squibb and Pfizer submitted that the page was misleading and could imply that once-daily novel oral anticoagulants (NOACs) (such as Xarelto) offered improved compliance vs twice-daily NOACs (such as Eliquis).

A disclaimer stated 'Not based on Xarelto data'. This page was referenced to Coleman *et al* (2012) which evaluated adherence rates of chronic cardiovascular therapy based on three criteria (taking adherence, regimen adherence, timing adherence). However, Bayer used the timing adherence results only, where the difference between once-daily and twice-daily dosing was the largest. The other two adherence results were not included on the page, and therefore this data had been generalised implying that these results referred to overall treatment adherence. Furthermore, Coleman *et al* indicated several limitations to their analysis. Bristol-Myers Squibb and Pfizer considered that the claim could [sic] be substantiated and therefore should not be used.

The Panel noted that page 6 was headed 'Compliance matters' and sub-headed 'Once-daily dosing improves compliance …'. This was followed by a chart which showed that 76.3% of patients complied with once-daily dosing vs 50.4% with twice-daily dosing. A highlighted box to the right-hand side of the chart featured the claim '25% increase in treatment adherence in once-daily vs twice-daily regimens'. The chart and claim were

based on the results of Coleman *et al*, a pooled analysis of 29 studies of patients taking chronic cardiovascular therapy including anticoagulants. The x axis of the chart was labelled 'Dosing frequency – Not based on Xarelto data'. In the Panel's view, given the context in which it appeared, the chart implied that it had been unequivocally shown that 76.3% of patients would comply with once-daily Xarelto therapy vs 50.4% of patients taking a twice-daily alternative. This was not so; the Panel considered that such an implication was misleading and could not be substantiated. A breach of the Code was ruled. The Panel considered that high standards had not been maintained and a breach of the Code was ruled.

Bristol-Myers Squibb and Pfizer noted the claim on page 8, 'Xarelto provides simple, proven, predictable anticoagulation for stroke prevention in non-valvular AF'. As stated above, 'simple' in that context inferred an all-embracing general claim and suggested that Xarelto was simple to use. Bristol-Myers Squibb and Pfizer submitted that this underplayed the complexity of anticoagulation treatment. Furthermore, the page demonstrated further 'cherry picking' of positive (superior vs warfarin) secondary endpoints with omission of important and relevant safety endpoints as previously mentioned. It mentioned protection against stroke and systemic embolism but did not state this was non-inferior to warfarin which was the primary endpoint of the study or that major bleeding was non-inferior to warfarin.

The Panel noted that page 8 was headed 'When it really matters' followed by the sub-heading 'Xarelto provides simple, proven, predictable anticoagulation for stroke prevention in non-valvular AF'. The first bullet point 'Simplicity matters' referred to the once-daily dosage with no adjustment needed for age, gender or body weight. The Panel considered its comments above applied here. The Panel did not consider that 'simple' was an all-embracing claim as alleged; it was clearly linked to the Xarelto dosage regimen details of which appeared immediately beneath. No breach of the Code was ruled. The Panel did not consider that Bayer had failed to maintain high standards and ruled accordingly.

The Panel noted the general allegation of 'cherry picking' of positive data for Xarelto vs warfarin and the omission of important and relevant safety endpoints. The Panel considered that the presentation of positive data without reference to endpoints where Xarelto was 'non-inferior' to warfarin was not necessarily unacceptable. In the Panel's view page 8 did not imply that Xarelto was more efficacious than warfarin; it highlighted some areas where Xarelto had a better safety profile vs warfarin and it referred to the dosage regimen of Xarelto. The Panel, however, noted its comments above about the increased risk of bleeding from GI sites with Xarelto vs warfarin. The bullet point on page 8 entitled 'Safety profile matters' referred to the decreased risk of fatal bleeds and of devastating inter-cranial haemorrhage with Xarelto vs warfarin but not to the increased risk of bleeding from GI sites. In the Panel's view, although Patel *et al* 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 bleeds vs patients on warfarin; the health professionals could thus manage that risk appropriately. The Panel considered that page 8 was misleading in that regard and a breach of the Code was ruled. The Panel considered that Bayer had failed to maintain high standards and ruled a breach of the Code.

Bristol-Myers Squibb and Pfizer complained about an Xarelto (rivaroxaban) exhibition panel (ref L.GB.02.2013.1694c, April 2013) and promotional booklet (ref L.GB.02.2013.1576c, February 2013) used by Bayer at the Eurostroke Conference in London in May. Bristol-Myers Squibb and Pfizer stated that use of certain claims should cease in all Xarelto materials exhibited at meetings, in all Xarelto advertising, and in any Xarelto promotional materials currently being used by Bayer.

Eliquis (apixaban) jointly marketed by Bristol-Myers Squibb and Pfizer and Xarelto were both anticoagulants indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Bayer explained that atrial fibrillation (AF) was the most common condition which caused irregular heartbeat. The collecting chamber of the heart ie the atrium beat irregularly and caused blood to stagnate in the atrial appendage, as a consequence of this the blood clotted in the atrial appendage. When all or part of this clot broke away, it could lodge in any blood vessel and block blood supply resulting in death of the affected tissue. The brain was the main organ affected, 15 to 20% of the strokes were associated with AF. Stroke was a devastating event particularly if it was associated with AF. Strokes associated with AF were bigger in size and patients had a 50% likelihood of death within one year.

Adequate anticoagulation could reduce the relative risk of having a stroke by 62%. Guidelines from the National Institute of Health and Care Excellence (NICE) and the European Society of Cardiology (ESC) recommended that patients with high risk of stroke should be anticoagulated. Warfarin had been the gold standard up until now but had always been perceived as difficult to manage due to the requirement of regular monitoring, drug and food interactions. There had always been a desire to have options which were at least as efficacious as warfarin but at the same time simple and convenient to use both by physician and patients. The recent development and approval of three novel oral anticoagulants, (NOACs) had increased treatment options. Other conditions which commonly required anticoagulation were deep vein thrombosis (DVT) and pulmonary embolism (PE). Heparin in combination with warfarin was used to prevent and treat these conditions. Xarelto was the only NOAC which could be used to prevent and treat DVT and PE.

A Xarelto exhibition panel (ref L.GB.02.2013.1694c, April 2013)

1 Claim 'Xarelto … Highly Effective Protection From Day One'

Below the claim was a bar chart depicting the results of Patel *et al* (2011) which showed that Xarelto was non-inferior compared with warfarin in the prevention of stroke and systemic embolism.

COMPLAINT

Bristol-Myers Squibb and Pfizer alleged that the claim was exaggerated and could not be substantiated. Whilst Xarelto might exhibit some Factor Xa (FXa) inhibition on day one (based on 2-3 half lives to reach steady state), 'protection' implied that strokes could be prevented on day one which could not be substantiated. Additionally 'highly effective' from day one was also exaggerated and could not be substantiated.

Bristol-Myers Squibb and Pfizer alleged breaches of Clauses 7.4 and 7.10.

RESPONSE

Bayer submitted that the validity of the claim 'Highly Effective Protection From Day One' rested on the interpretation of 'highly effective protection' and whether that was deliverable from the first day of treatment.

Pfizer and Bristol-Myers Squibb had complained on the basis that 'protection' implied that strokes could be prevented on day one which could not be substantiated' and that 'highly effective' was an exaggerated claim that could not be substantiated

Bayer submitted that the claim was in line with the Xarelto summary of product characteristics (SPC), opinion from the Committee for Medicinal Products for Human Use (CHMP), published literature and was supported by the mechanism of action, pharmacokinetics and pharmacodynamics of Xarelto. In addition, Xarelto had been shown to be non-inferior to warfarin, the gold standard AF treatment.

Bayer noted that as the target audience at the Eurostroke conference were specialists in stroke, it was reasonable to assume that they had a good understanding of the available treatments and were unlikely to be easily misled. Bayer submitted that 'protection' did not imply that all strokes would be prevented on day one; no product was 100% effective and certainly not on the first day of dosing. For this target audience, 'protection' could reasonably be understood to mean that the product worked from day one to reduce the risk of stroke in line with its licensed indication. Further, Xarelto was highly effective and this was supported with a strong evidence base.

In support of the above, Bayer submitted that the Atrial Fibrillation Association (AFA) booklet published in 2008 (reviewed 2012) and endorsed by the Department of Health (DoH), stated that new oral anticoagulants were effective almost immediately after taking, and large clinical trials had shown them to be as effective as warfarin in reducing the risk of stroke.

Sections 5.1 and 5.2 of the Xarelto SPC stated, 'Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi'. Protection against atrial fibrillation was achieved by inhibiting Factor Xa, in atrial fibrillation sluggish flow in the left atrium predisposed to clot formation in the atrial appendage which could embolise to brain vessels and cause stroke. Successful prevention of stroke was achieved by reducing the creation of thrombi.

Kubitza *et al* (2005a) stated 'Maximum inhibition of FXa activity was achieved 1 to 4 hours after administration of [Xarelto].'

The Xarelto SPC further stated 'In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for prothrombin time (Neoplastin) 1-4 hours after tablet intake (ie at the time of maximum effect) in patients treated with 20mg once-daily ranged from 14 to 40s'.

Kubitza *et al* (2005b) showed that in healthy caucasian males 'Maximum inhibition of FXa activity occurred approximately 3h after [Xarelto] dosing. Following the first dose of [Xarelto], maximum inhibition of FXa activity was 22% after 5mg, 33% after 10mg, 56% after 20mg, and 68% after 30mg, and inhibition was maintained for 8–12h after 5mg and for approximately 12h after the 10mg, 20mg, and 30mg doses. There were no major differences in maximum inhibition of FXa activity between the first and second daily doses, or on day 7 compared with day 0, although trough levels were increased with the 20mg and 30mg bid doses'. 'The onset of inhibition of FXa activity with [Xarelto] was rapid, with maximum effect occurring within 2–3 hours of dosing in all dosing groups'.

Graff *et al* (2007) in a placebo-controlled, randomised, crossover study in 12 healthy subjects showed maximal effect of Xarelto 2 hours after administration: prothrombinase-induced clotting time was prolonged 1.8 and 2.3 times baseline after Xarelto 5mg and 30mg, respectively. Collagen-induced endogenous thrombin potential was reduced by ~80% and ~90% compared with baseline after Xarelto 5mg and 30mg, respectively, and tissue factor-induced endogenous thrombin potential was reduced by ~40% (5mg) and ~65% (30mg), respectively. Thrombin generation remained inhibited for 24 hours'.

In contrast, the mechanism of action for warfarin was different and slow to make the desired effect. Warfarin inhibited synthesis of vitamin K dependent coagulation factors and the warfarin SPC stated, 'An anticoagulation effect generally occurs within 24 hours after drug administration. However, peak anticoagulant effect may be delayed 72 to 96 hours'. There was no such lag time for Xarelto

and maximum concentration (C_{max}) appeared 2-4 hours after oral intake. Warfarin inhibited natural anticoagulants like protein C and S in addition to sequential depression of vitamin K dependent anticoagulation factors (Factors VII, IX, X and II) activities, hence the need for bridging with heparin. There was no such requirement for Xarelto, which was a specific direct FXa inhibitor and was acknowledged by the CHMP committee.

The European Medicines Agency (EMA) in its assessment report for Xarelto (22 September 2011 ref EMA/CHMP/301607/2011), under the section 'Final dose regimen chosen' stated that 'It was therefore determined that including b.i.d. dosing initially in the Xarelto regimen for the phase III program could provide the intensification needed and permit continuous Xarelto therapy without first requiring the use of a heparin in the initial acute DVT treatment phase'. Section 2.5.3, 'Discussion on clinical efficacy', stated 'It is, however, agreed with the Applicant that there is little evidence that supports a general recommendation for the use of parenteral anticoagulants in the initial phase of acute treatment. The similar time of onset after administration of the two anticoagulants is of vital importance for this conclusion'. The assessment report dated 22 September 2011 (ref EMA/42547/2012) agreed the same assumption for stroke prevention in atrial fibrillation for dose finding; 'These simulations showed that the simulated plasma Xarelto concentration-time profile for patients in the [stroke prevention in atrial fibrillation] patient population with normal renal function receiving 20mg once-daily was similar to that for patients in the DVT-T population receiving the same dose'.

This demonstrated that the CHMP did not consider the requirement of heparin for Xarelto to bridge the initial period and considered it effective from day one.

Patel *et al* and other similar trials for NOACs were event driven, non-inferiority trials. It was expected in event driven trial design that patients would have events to compare therapies in a randomised control trial. These trials were not powered to show results on a daily basis and meaningful results were obtained on the pre-specified number of events. In such trials, the primary endpoint achieved statistical significance. The Xarelto SPC stated, 'Xarelto was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism'.

The fact that warfarin was highly effective in preventing stroke in patients with atrial fibrillation was well recognised in published literature including pivotal studies like Patel *et al*, Granger *et al* (2011), and many others like Shameem and Ansell (2013); Albertsen *et al* (2013); Halperin and Goyette (2012); Clase *et al* (2012); Quinn *et al* (2012); Jorgensen *et al* (2012); Mangiafico and Mangiafico (2012); Martin and Stewart (2012); Chan *et al* (2011), to cite a few from recent years.

Patel *et al* clearly showed that rivaroxaban was non-inferior to warfarin in the intention to treat (ITT) population and superior to warfarin in the per-protocol (PP) population, making it highly effective.

In summary, Xarelto was demonstrably non-inferior to the gold standard (warfarin) in its effectiveness (protection against stroke) and the mode of action delivered that protection (coagulation inhibition) within hours of the first dose. Bayer thus submitted that these claims were not exaggerated and could be substantiated and were not in breach of Clauses 7.4 and 7.10.

PANEL RULING

The Panel noted that the claim at issue appeared below the headline 'Efficacy matters:' and was followed by a bar chart which compared the efficacy of Xarelto with that of warfarin. The bar chart depicted the results of Patel *et al* and showed that Xarelto was non-inferior to warfarin for the primary endpoint of stroke or systemic embolism. Study participants were followed for a median of 707 days. In the per-protocol population, stroke or systemic embolism occurred in 188 patients in the Xarelto group (1.7% per year) and in 241 patients in the warfarin group (2.2% per year) ($p<0.001$ for non-inferiority).

The Panel noted Bayer's submission that the anticoagulant effect of Xarelto was due to its inhibition of FXa and that maximum inhibition (and C_{max}) occurred within hours of dosing. Warfarin exerted its anticoagulant effect by inhibiting the synthesis of vitamin K dependent coagulation factors. Although anticoagulation effects occurred within 24 hours of warfarin administration, peak anticoagulation might be delayed 72 to 96 hours. The Panel acknowledged that inhibition of FXa would prevent clotting and thus protect patients from stroke and systemic embolism and in that regard, Xarelto exhibited maximum inhibition on day one. Nonetheless, efficacy of Xarelto was measured in terms of the prevention of stroke and systemic embolism – inhibition of FXa was a pharmacological effect and not, in itself, a measure of efficacy. In the Panel's view, the claim at issue, under the heading 'Efficacy matters:' implied that on day one, Xarelto had been shown to have a direct measurable effect on the prevention of stroke and systemic embolism. This was not so. The Panel considered that the claim could not be substantiated. A breach of Clause 7.4 was ruled. The Panel further considered that the claim was exaggerated. A breach of Clause 7.10 was ruled.

B Xarelto promotional booklet (L.GB.02.2013.1576c, February 2013)

1 'A reassuring safety profile matters'

This statement appeared as the heading to page 4 above a bar chart which detailed safety data from Patel *et al*.

COMPLAINT

Bristol-Myers Squibb and Pfizer submitted that only favourable secondary endpoints had been given prominence on page 4 of the booklet. It was not clear that the primary endpoint (stroke and systemic embolism) was non-inferior to warfarin. The primary safety analysis in Patel *et al*, 'major and non-major

clinically relevant bleeding' and the safety endpoint, 'major bleeding', had not been included. Both of these endpoints showed no significant difference for Xarelto vs warfarin, and by omitting them clinicians were not presented with a fair and balanced overview of the safety analysis; Bristol-Myers Squibb and Pfizer alleged that Bayer had 'cherry picked' favourable data. In an inter-company letter Pfizer alleged a breach of Clauses 7.2 and 9.1.

Page 4 further stated that there were more gastrointestinal bleeds vs warfarin but there was no quantification of the increased risk or p-values to demonstrate that the increased risk was statistically significant, which it was. During inter-company correspondence Bayer agreed to add a p-value for the gastrointestinal bleeding data in future materials. However, Bayer had not agreed to present the event rates or hazard ratio in materials. Bristol-Myers Squibb and Pfizer submitted that the presentation of event rates or hazard ratios was important so that clinicians could correctly interpret that important safety endpoint. In an inter-company letter Pfizer alleged a breach of Clause 7.2.

During inter-company correspondence, Bayer agreed not to use the title of this page 'A reassuring safety profile matters'. However, Bristol-Myers Squibb and Pfizer were concerned about the claim further down the page 'Even in your fragile patients, Xarelto has an established safety profile'. The supplementary information to Clause 7.9 stated that 'The restrictions on the word "safe" apply equally to grammatical derivatives of the word such as "safety". For example, "demonstrated safety" or "proven safety"are prohibited under this clause'. In an inter-company letter Pfizer alleged a breach of Clause 7.9.

Bristol-Myers Squibb and Pfizer were concerned about the reference to 'Even in your fragile patients'. The statement regarding renally impaired patients (an example of 'fragile' patients) was inconsistent with the Xarelto SPC and underplayed the safety data. The SPC stated that in moderate renal impairment the dose of Xarelto had to be reduced to 15mg once-daily. In severe renal impairment it had to be used with caution. Xarelto was not recommended if creatinine clearance was <15ml/min. Because of increased risk of bleeding, careful monitoring for signs/symptoms of bleeding complications and anaemia was required after treatment initiation in patients with severe renal impairment (creatinine clearance 15-29 ml/min) or with moderate renal impairment (creatinine clearance 30-49 ml/min) concomitantly receiving other medicinal products which increased rivaroxaban plasma concentrations.

The elderly population was also highlighted as a potential 'fragile' patient population. However, in the elderly there was a high prevalence of renal impairment and so the above concerns highlighted for renal impairment also applied to a 'fragile' elderly population. To refer to an established safety profile in these 'fragile' patients was misleading and the safety claim could not be substantiated. In an inter-company letter Pfizer alleged a breach of Clauses 7.9 and 9.1.

In their complaint to the Authority, Bristol Myers Squibb and Pfizer summarised their concerns about the booklet as a whole and referred to: Clause 7.2 (misleading by 'cherry picking' favourable data); Clause 7.4 (claims not capable of substantiation); Clause 7.9 (safety claims not capable of substantiation and safety underplayed); Clause 7.10 (exaggerated and all-embracing claims) and Clause 9.1 (high standards not maintained).

REPSONSE

Bayer noted that Pfizer and Bristol-Myers Squibb had outlined a number of comments in relation to this page. However, Bayer failed to identify a single allegation in relation to a specific clause number. Clause 7.9 was mentioned but there was no allegation, as such. Pfizer and Bristol-Myers Squibb implied that statements such as 'proven safety' or 'demonstrated safety' were not acceptable, however Bayer had not used either of these statements in its claim. Bayer's claim was: 'Even in your fragile patients, Xarelto has an established safety profile'. This clearly referred to the overall data set available for patients in those sensitive groups, rather than a claim for the product *per se*.

Bayer noted Pfizer and Bristol-Myers Squibb's concern that the data had been 'cherry picked' because the primary endpoint (non-inferiority) was not made clear, however, there was no specific complaint on that point. Even if there were, the claims on page 4 were about safety. Since Patel *et al* showed non-inferiority, the products were comparable in terms of efficacy and therefore presenting the differences in respect of safety was not misleading (had the study failed to show non-inferiority, that might have been a different matter).

Bayer noted that Pfizer and Bristol-Myers Squibb had further commented that the presentation of p-values, hazard ratios and event rates was helpful to the reader; Bayer did not disagree, however there was no Code requirement *per se* to present those statistical reference points. Bayer submitted that it had provided all the safety information which a clinician needed to make an informed decision. Bayer agreed to include the p-value for gastrointestinal bleeding during inter-company dialogue as it was statistically significant but it was not a requirement of the Code to include p-values and event rates for each result.

Bayer noted that Pfizer and Bristol-Myers Squibb did not identify a specific clause number, but had commented generally about the phrase: 'Even in your fragile patients, Xarelto has an established safety profile'.

Bayer stated that Xarelto had an established safety profile in fragile patients. There was no claim that the product was 'safe' in this group, and no inference that it should be prescribed at the standard dose; only that the track record in this population was positive. In fact it was specifically noted in the SPC that in AF patients with moderate renal impairment and severe renal impairment, a reduction in dose was appropriate. As stated, many elderly patients

had a degree of renal impairment; however the elderly (*per se*) was not identified as a risk group for Xarelto; the SPC clearly identified patients in whom caution was appropriate because they were renally impaired, regardless of age.

The safety information in the booklet was based on 187 clinical trials in more than 90,000 patients (Bayer IMPACT database) and worldwide clinical use by over 5 million patients.

The EMA in its assessment report for Xarelto (22 September 2011 ref EMA/CHMP/ 301607/2011), considered the evidence (in the 'Special populations' section) and agreed, 'The increased exposure in the elderly was to a large extent caused by reduced renal function. Consequently dose reduction based on age alone was not considered needed. The [stroke prevention in atrial fibrillation] population consisted mostly of elderly patients and there was extensive experience in treating elderly patients with Xarelto 20mg q.d'.

Contrary to other NOACs, the Xarelto SPC placed no dose restriction for use in elderly patients.

The Eliquis SPC referred to use in the elderly and stated 'No dose adjustment required, unless criteria for dose reduction are met'. With regard to dose reduction the SPC stated 'The recommended dose of Eliquis is 2.5mg [instead of 5mg] taken orally twice-daily in patients with [non-valvular atrial fibrillation] and at least two of the following characteristics: age ≥ 80 years, body weight ≤60kg, or serum creatinine ≥1.5mg/dl (133micromole/l)'.

The Pradaxa SPC stated that the recommended daily dose was 220mg (instead of 300mg) taken as one 110mg capsule twice-daily in patients aged 80 years or above. For patients aged between 75 and 80, the daily dose of Pradaxa of 300mg or 220mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding.

Halperin *et al* (unknown date) presented the sub-analysis of Patel *et al* and concluded, 'In elderly, high-risk patients with AF, once-daily oral rivaroxaban without coagulation monitoring or dose adjustment performed favourably compared to adjusted-dose warfarin as it did in the overall [study] population'. Halperin stated no need for Xarelto dose adjustment.

With regard to renal patients Xarelto had an established safety profile as in Patel *et al* the pivotal phase III trial for Xarelto, a cohort of patients with impaired renal failure were studied with lower dose of 15mg instead of 20mg. The lower dose of Xarelto (15mg once a day) was evidence based (a large phase III clinical trial), in line with the Xarelto SPC and did not underplay the safety data.

The Xarelto SPC stated 'In patients with moderate (creatinine clearance 30-49ml/min) or severe (creatinine clearance15-29ml/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 (see section 5.2)'.

Fox *et al* (2011) published the sub-analysis of Patel *et al* renal impairment patients and stated 'Dose adjustment in [Patel *et al*] yielded results consistent with the overall trial in comparison with dose-adjusted warfarin'. Fox *et al* further quoted in the safety section that, 'there was no excess bleeding on rivaroxaban compared with warfarin. There was no excess in the principal safety endpoint (HR 0.98; 95% CI 0.84–1.14) or in the individual bleeding outcomes in those treated with rivaroxaban 15mg/day compared with dose-adjusted warfarin. Furthermore, in those with moderate renal insufficiency, critical organ bleeding (HR 0.55; 95% CI 0.30–1.00) and fatal bleeding (HR 0.39; 95% CI 0.15–0.99) were less frequent with rivaroxaban. The lower rate of fatal bleeding was consistent with the findings in those with preserved renal function (HR 0.55; 95% CI 0.32–0.93)'. Fox *et al* further stated that 'In patients with moderate renal insufficiency, rivaroxaban-treated patients had more frequent gastrointestinal bleeding (4.1 vs. 2.6%; p = 0.02)'.

The safety profile of Xarelto for elderly patients and patients with renal impairment was in line with the SPC and established with good clinical evidence.

PANEL RULING

The Panel noted Bayer's assertion that the complainants had not alleged breaches of any specific clauses of the Code. The Panel further noted, however, that inter-company dialogue clearly referred to relevant clauses of the Code and so the Panel used this as the basis for its ruling. In addition, specific clauses of the Code were listed in the summary of the complaint.

The Panel noted that the booklet at issue was entitled 'Anticoagulation: why Xarelto matters'. Pages 2 and 3 introduced the reader to Xarelto, its four licensed indications and that it was now widely prescribed. Page 4 was 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 the safety data from Patel *et al* which compared Xarelto and warfarin. The principle 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 gastrointestinal sites occurred more frequently in the Xarelto group (3.2% vs 2.2%, p<0.001).

The Panel noted the allegation that the page at issue did not refer to the primary [efficacy] endpoint (stroke and systemic embolism) or make it clear that this endpoint was non-inferior to warfarin. The Panel noted that the page at issue dealt with safety issues of the two medicines and featured a bar chart which depicted bleeding events where there was a

significant advantage for Xarelto vs warfarin. In that regard the Panel did not consider that the lack of efficacy data was misleading, particularly when that data showed Xarelto to be non-inferior to warfarin. In the Panel's view, health professionals would not be misled into prescribing a product which Bayer claimed to have a 'reassuring safety profile' but which was less efficacious than the competitor to which it was compared. No breach of Clause 7.2 and 9.1 was ruled.

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'. The Panel noted that during inter-company dialogue Bayer had agreed to add the p-value to the claim in question and thus this matter was not considered by the Panel. The Panel noted however, 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 was ruled.

The Panel noted the claim 'Even in your fragile patients, Xarelto has an established safety profile'. In the Panel's view the claim did not imply that Xarelto was safe to use in fragile patients – it referred to the safety profile of the medicine and was not an absolute claim for safety. The Panel ruled no breach of Clause 7.9. The Panel considered that the claim could be substantiated and no breach of Clause 7.4 was ruled. Given these two rulings, the Panel also ruled no breach of Clause 9.1.

The Panel noted that following the claim about fragile patients, those with moderate to severe renal impairment and the elderly (≥75 years) were listed as examples of such patients. With regard to renal impairment, the Panel noted that Xarelto could be prescribed to those with a creatinine clearance of 15ml/min (severe renal impairment) or more. The medicine was not recommended for patients with a creatinine clearance of <15ml/min (renal failure). The Panel further noted the reference to elderly patients as a separate group and that many of them would have some degree of renal impairment. Age alone, however, was not a reason to reduce the dose of Xarelto. As above, the Panel did not consider that the reference to an established safety profile in the elderly or those with moderate or severe renal impairment was a claim for absolute safety in either group. No breach of Clause 7.9 was ruled. The Panel considered that the claim could be substantiated; no breach of Clause 7.4 was ruled. The Panel also ruled no breach of Clause 9.1.

2 'Simplicity matters'

This statement appeared as the heading to page 5.

COMPLAINT

Bristol-Myers Squibb and Pfizer alleged that page 5 underplayed the complexity of anticoagulation treatment for patients and clinicians, whereby stroke prevention had to be balanced against the risk of bleeding. During inter-company correspondence Bayer referred to Case AUTH/2537/10/12 - Anonymous v Bayer, where Bayer was not found in breach for the claim 'one tablet, once-daily, simple'. However, the page title was a very different claim to the one in the case report. Bristol-Myers Squibb and Pfizer alleged that the heading 'Simplicity matters' was an all-embracing, general claim. Bristol-Myers Squibb and Pfizer considered that the implication was that using Xarelto to manage a patient's anticoagulation was a simple matter. Furthermore, in the Xarelto SPC it stated 'Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period'. Bristol-Myers Squibb and Pfizer were concerned that the page could imply that once Xarelto was prescribed, few other considerations were needed as it was so simple. In an inter-company letter Pfizer alleged a breach of Clauses 7.9 and 9.1.

Page 5 also included the claim 'Once-daily Xarelto provides fast-acting, 24 hour protection'. As described above, Bristol-Myers Squibb and Pfizer did not consider that it could be adequately substantiated and was an exaggerated claim. Pharmacodynamic studies of FXa inhibition could not be extrapolated to imply 'fast acting' stroke prevention. In an inter-company letter Pfizer alleged a breach of Clauses 7.4 and 7.10.

In their complaint to the Authority, Bristol Myers Squibb and Pfizer summarised their concerns about the booklet as a whole and referred to: Clause 7.2 (misleading by 'cherry picking' favourable data); Clause 7.4 (claims not capable of substantiation); Clause 7.9 (safety claims not capable of substantiation and safety underplayed); Clause 7.10 (exaggerated and all-embracing claims) and Clause 9.1 (high standards not maintained).

RESPONSE

Bayer noted that Pfizer and Bristol-Myers Squibb had not identified any clauses of the Code in relation to the above and so Bayer's comments were of a general nature in the absence of any specific allegation.

Some general points had been made by Pfizer and Bristol-Myers Squibb, however their comments were not correct and out of context.

The page had two bold headings under the main heading of 'Simplicity matters'; 'A once-daily novel oral anticoagulant that provides 24hr protection…' and '…without the need to adjust dose for a patient's age, gender or body weight'.

Bayer noted that Pfizer and Bristol-Myers Squibb discussed the claim: 'Once-daily Xarelto provides fast-acting, 24-hour protection'. As already indicated, Xarelto had an inhibitory effect within hours of the first dose, had demonstrated 24-hour duration of action and in inhibiting FXa, worked to reduce the risk of stroke in line with the licensed indication; the claim did not imply that strokes were prevented quickly. The argument for 'fast acting'

had been discussed earlier. '24-hour protection' was based on the results of clinical trials, and a brief account was given below.
In Patel *et al*, a once-daily dose was used to provide protection to patients and was shown to be non-inferior to warfarin. Warfarin reduced the relative risk of stroke in patients with atrial fibrillation by 62%. The evidence that Xarelto was superior to warfarin in per-protocol analysis and non-inferior to warfarin in ITT analysis, demonstrated that once-daily Xarelto provided protection for 24 hours. No other NOAC had shown benefit of once a day dose in a clinical trial.

The EMA in its assessment report for Xarelto (22 September 2011 ref EMA/CHMP/301607/2011), stated 'Another study identified a prolonged influence of rivaroxaban beyond 24h on the peak level of the [endogenous thrombin potential] as well as lag time suggesting that pharmacological effects may be present beyond 24 hours after doses of 20mg'.

Graff *et al* stated 'Thrombin generation remained inhibited for 24 hours'.

Both claims on page 5 were in line with the Xarelto SPC, which stated, that in the indication of stroke prevention in patients with non-valvular atrial fibrillation, the randomised controlled trial was designed to show efficacy at once a day dose. The results demonstrated that once a day dose was non-inferior to warfarin. It also stated that no dose adjustment was required for patient's age, gender or body weight. These were in contrast to other available NOACs, which were taken twice a day and needed dose adjustment for age and body weight.

The Xarelto SPC stated that 'The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. In the pivotal double-blind [Patel *et al*] study, 14,264 patients were assigned either to Xarelto 20mg once-daily (15mg once-daily in patients with creatinine clearance 30 - 49ml/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months'.

'Xarelto was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism. In the per-protocol population on treatment, stroke or systemic embolism occurred in 188 patients on rivaroxaban (1.71% per year) and 241 on warfarin (2.16% per year) (HR 0.79; 95% CI, 0.66 – 0.96; p<0.001 for non-inferiority). Among all randomised patients analysed according to ITT, primary events occurred in 269 on rivaroxaban (2.12% per year) and 306 on warfarin (2.42% per year) (HR 0.88; 95% CI, 0.74 – 1.03; p<0.001 for non-inferiority; p=0.117 for superiority)'.

The Xarelto SPC stated that there was no dose adjustment for the elderly population or for body weight or gender.

The Elequis SPC stated that a dose reduction was required if at least two of the following characteristics were present: age ≥80 years, body weight ≤60kg, or serum creatinine ≥1.5mg/dl (133micromole/l).

The Pradaxa SPC recommend close clinical surveillance in patients with a body weight <50kg. Xarelto was simple to use. The Panel had ruled on this general point in Case AUTH/2537/10/12. The claims on page 5 were in line with both the SPC and CHMP opinion. Consequently they could be substantiated and were therefore not in breach of the Code.

PANEL RULING

The Panel noted its comments at point B1 above regarding the citation of specific clauses in the complaint and considered that they applied here.

The Panel noted that page 5 was headed 'Simplicity matters' and sub-headed in emboldened text, 'A once-daily novel oral anticoagulant that provides 24hr protection …'. The sub-heading continued further down the page with '… without the need to adjust dose for a patient's age, gender or body weight' which was similarly emboldened. There then followed a description of the dosage regimen; one 20mg tablet once-daily (with food) for patients with atrial fibrillation and one 15mg tablet once-daily (with food) for atrial fibrillation patients with moderate or severe renal impairment. The Panel noted that the heading 'Simplicity matters' was on a page which clearly dealt with the once-daily dosing regimen of Xarelto. The Panel considered that the intended audience (nurses, payors, pharmacists and physicians) would be well acquainted with the complexities of treating patients with warfarin. The dosing regimen and monitoring of Xarelto patients was not as complicated as warfarin therapy. In the Panel's view, health professionals would know that with any anticoagulant, the risk of unintended bleeding had to be balanced against stroke prevention. The Panel did not consider that 'Simplicity matters' underplayed the complexity of anticoagulant therapy as alleged. No breach of Clause 7.9 was ruled. The Panel also ruled no breach of Clause 9.1.

With regard to the claim 'Once-daily Xarelto provides fast-acting, 24 hour protection', the Panel noted its comments at point A1 above. The Panel considered that, contrary to Bayer's submission, the claim implied that Xarelto had been shown to have a fast and measurable effect on the prevention of stroke and systemic embolism. In the Panel's view this was not so. The Panel thus considered that the claim was exaggerated as alleged. A breach of Clause 7.10 was ruled. The Panel further considered that the claim could not be substantiated and a breach of Clause 7.4 was ruled.

3 'Compliance matters'

This statement appeared as a heading to page 6.

COMPLAINT

Bristol-Myers Squibb and Pfizer noted that the sub-heading to page 6 was, 'Once-daily dosing improves

compliance ...'. Bristol-Myers Squibb and Pfizer submitted that the page was misleading and could imply that once-daily NOACs (such as Xarelto) offered improved compliance vs twice-daily NOACs (such as Bristol-Myers Squibb /Pfizer's Eliquis).

A disclaimer stated 'Not based on Xarelto data'. This page was referenced to Coleman *et al* (2012) which evaluated adherence rates of chronic cardiovascular therapy based on three criteria (taking adherence, regimen adherence, timing adherence). However, Bayer had chosen to use the timing adherence results only, where the difference between once-daily and twice-daily dosing was the largest. The other two adherence results were not included on the page, and therefore this data had been generalised implying that these results referred to overall treatment adherence. Furthermore, Coleman *et al* indicated several limitations to their analysis such as inclusion of studies of small sample size, populations with differing cardiovascular disease states resulting in statistical heterogeneity, publication bias, and exclusion of studies with missing information that the authors were unable to obtain following request.

In summary, Bristol-Myers Squibb and Pfizer considered that the claim 'Once-daily dosing improves compliance...' (by implication compared with the competitor NOACs which were twice-daily) could [sic] be substantiated and therefore should not be used.

In an inter-company letter Pfizer alleged a breach of Clauses 7.2, 7.4 and 9.1.

In their complaint to the Authority, Bristol Myers Squibb and Pfizer summarised their concerns about the booklet as a whole and referred to: Clause 7.2 (misleading by 'cherry picking' favourable data); Clause 7.4 (claims not capable of substantiation); Clause 7.9 (safety claims not capable of substantiation and safety underplayed); Clause 7.10 (exaggerated and all-embracing claims) and Clause 9.1 (high standards not maintained).

RESPONSE

Bayer noted that Pfizer and Bristol-Myers Squibb had made some very general comments about page 6, however there were no specific clauses cited so Bayer could not respond to any specific allegations.

Bayer stated that it appeared that Pfizer and Bristol-Myers Squibb regarded the page as a comparison of once-daily Xarelto and twice-daily Eliquis.

Bayer stated that it had not made any comparison with other NOACs on page 6. The comparison to Eliquis was an assumption by Pfizer and Bristol-Myers Squibb. This section clearly stated that once a day improved compliance and this could be substantiated by many publications including research supported by Pfizer and Bristol-Myers Squibb.

Literature review and meta-analysis supported by Pfizer and Bristol-Myers Squibb and published in Patient Preference Adherence, in May 2013 concluded that 'Current meta-analyses suggested that across acute and chronic disease states, reducing dosage frequency from multiple dosing to [once-daily] dosing may improve adherence to therapies among patients. Improving adherence may result in subsequent decreases in health care costs' (Srivastava *et al* 2013).

Renda and Caterina (2013) evaluated NOACs in atrial fibrillation and concluded, 'Indeed, a new oral anticoagulant that is proven to be effective and safe with a once-daily dosing is usually advantageous over other agents that need two administrations per day, with respect to drug adherence and patients' as well as physicians' acceptance'.

The EMA in its assessment report for Xarelto (22 September 2011 ref EMA/CHMP/301607/2011), under the section 'Final dose regimen chosen' accepted the argument of selection of a once a day dose based on phase II data and the advantage of patient convenience and compliance, 'In the phase II dose-finding studies, there was no dose response relationship or clear efficacy advantage observed for [twice-daily] dosing compared with [once-daily] dosing over the range of rivaroxaban doses tested, and no definitive difference between the [twice-daily] and [once-daily] regimens was seen in bleeding compared to [low molecular weight heparin-vitamin K antagonist], except at 40mg [three times a day] or higher. The [once-daily] dosing was considered advantageous from a patient convenience and compliance perspective'.

Bayer did not agree with Pfizer and Bristol-Myers Squibb's concern regarding Coleman *et al* and selection of timing adherence. Bayer noted that the authors mentioned that this was the first systematic review and meta-analysis published in literature to evaluate the effect of dosing frequency on chronic medication adherence and included prospectively collected data of 18 randomised clinical trials and 11 observational studies. The systematic review included clinical trials on anticoagulants. Adherence was measured by three definitions; taking adherence, regimen adherence and timing adherence. All definitions showed that that adherence was significantly improved by once-daily dosing ($p<0.01$ for all definitions of adherence). Bayer quoted from the publication 'Lastly, the percentage of near optimal inter-administration intervals was defined as timing adherence, which was the most stringent definition of adherence commonly used in the medical literature'.

Coleman *et al* also referred to the fact that simplifying the regimen with less frequent daily dosing seemed to be a reasonable intervention.

A similar recommendation was made by NICE in Medicine Adherence CG 76 with a suggested intervention of simplifying the dosing regimen.

The National Council on Patient Information and Education stated in its guidance, Enhancing Prescription Medicine Adherence: A National Action Plan, 'For many patients, one of the biggest

stumbling blocks to taking their medicines is the complexity of the regimen. Studies found that patients on once-daily regimens were much more likely to comply than patients who were required to take their medicine(s) multiple times each day'.

PANEL RULING

The Panel noted its comments at point B1 above regarding the citation of specific clauses in the complaint and considered that they applied here.

The Panel noted that page 6 was headed 'Compliance matters' and sub-headed 'Once-daily dosing improves compliance ...'. This was followed by a chart which showed that 76.3% of patients complied with once-daily dosing vs 50.4% with twice-daily dosing. A highlighted box to the right-hand side of the chart featured the claim '25% increase in treatment adherence in once-daily vs twice-daily regimens'. The chart and claim were based on the results of Coleman *et al*, a pooled analysis of 29 studies of patients taking chronic cardiovascular therapy including anticoagulants. The x axis of the chart was labelled 'Dosing frequency – Not based on Xarelto data'. In the Panel's view, given the context in which it appeared, the chart implied that it had been unequivocally shown that 76.3% of patients would comply with once-daily Xarelto therapy vs 50.4% of patients taking a twice-daily alternative. This was not so; the Panel considered that such an implication was misleading and could not be substantiated. A breach of Clauses 7.2 and 7.4 was ruled. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

4 'When it really matters'

This statement appeared as the heading to page 8.

COMPLAINT

Bristol-Myers Squibb and Pfizer noted the claim 'Xarelto provides simple, proven, predictable anticoagulation for stroke prevention in non-valvular AF'. As stated above, 'simple' in that context inferred an all-embracing general claim and suggested that Xarelto was simple to use. Bristol-Myers Squibb and Pfizer submitted that this underplayed the complexity of anticoagulation treatment. In an inter-company letter Pfizer alleged breaches of Clauses 7.9 and 9.1.

Furthermore, the page demonstrated further 'cherry picking' of positive (superior vs warfarin) secondary endpoints with omission of important and relevant safety endpoints as mentioned above. It mentioned protection against stroke and systemic embolism but did not state this was non-inferior to warfarin which was the primary endpoint of the study or that major bleeding was non-inferior to warfarin. In an inter-company letter Pfizer alleged a breach of Clauses 7.2 and 9.1.

In their complaint to the Authority, Bristol Myers Squibb and Pfizer summarised their concerns about the booklet as a whole and referred to: Clause 7.2 (misleading by 'cherry picking' favourable data); Clause 7.4 (claims not capable of substantiation); Clause 7.9 (safety claims not capable of substantiation and safety underplayed); Clause 7.10 (exaggerated and all-embracing claims) and Clause 9.1 (high standards not maintained).

Given its concerns, Bristol-Myers Squibb and Pfizer submitted that use of the above claims should cease in all Xarelto materials exhibited at meetings, in all Xarelto advertising, and in any Xarelto promotional materials currently being used by Bayer colleagues.

RESPONSE

Bayer noted that Pfizer and Bristol-Myers Squibb had discussed a number of points but had not specified any particular clause of the Code in relation to their concerns. The complainants had discussed the claim that 'Xarelto provides simple, proven, predictable anticoagulation ...'. Prior to the introduction of this latest class of anticoagulants, there were two main treatment options. These were injectable anticoagulants such as heparin and oral 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 called for dexterity which not all older patients had, if this was the case help from a carer or visit by a district nurse was necessary. In addition, sharps and needles had to be disposed of properly.

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. This point was made in the Rapid Response Report NPSA/2010/RRR018, 'Preventing fatalities from medication loading doses'. Table 2 in the report 'Medication involved in reported incidents' listed warfarin as the first of four critical medicines linked to loading dose errors.

The dose of warfarin needed to be adjusted to take account of changes in food, drinks and concomitant medications. 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 had an impact on lifestyle.

Considering this background of anticoagulation, NOACs were simple to use and Xarelto with a once-daily, simple regimen was convenient and easy to use. Bayer cited the fact that the CHMP, the Atrial Fibrillation Association (patient organisation), the European Society of Cardiology 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.

PANEL RULING

The Panel noted its comments at point B1 above regarding the citation of specific clauses in the complaint and considered that they applied here.

The Panel noted that page 8 was headed 'When it really matters' followed by the sub-heading 'Xarelto provides simple, proven, predictable anticoagulation for stroke prevention in non-valvular AF'. The first bullet point 'Simplicity matters' referred to the once-daily dosage with no adjustment needed for age, gender or body weight. The Panel noted its comments at point B2 above and considered that they applied here. The Panel did not consider that 'simple' was an all-embracing claim as alleged; it was clearly linked to the Xarelto dosage regimen details of which appeared immediately beneath. No breach of Clause 7.9 was ruled. The Panel also ruled no breach of Clause 9.1.

The Panel noted the general allegation of 'cherry picking' of positive data for Xarelto vs warfarin and the omission of important and relevant safety endpoints. The Panel considered that the presentation of positive data without reference to endpoints where Xarelto was 'non-inferior' to warfarin was not necessarily unacceptable. In the Panel's view page 8 did not imply that Xarelto was more efficacious than warfarin; it highlighted some areas where Xarelto had a better safety profile vs warfarin and it referred to the dosage regimen of Xarelto. The Panel, however, noted its comments at point B1 above about the increased risk of bleeding from GI sites with Xarelto vs warfarin. The bullet point on page 8 entitled 'Safety profile matters' referred to the decreased risk of fatal bleeds and of devastating inter-cranial haemorrhage with Xarelto vs warfarin but not to the increased risk of bleeding from GI sites. In the Panel's view, although Patel *et al* 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 bleeds vs patients on warfarin; the health professionals could thus manage that risk appropriately. The Panel considered that page 8 was misleading in that regard and a breach of Clause 7.2 was ruled. The Panel also ruled a breach of Clause 9.1.

Complaint received **1 November 2013**

Case completed **4 February 2014**