Response to:

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal consultation document

Rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation

Prepared by:

Bristol-Myers Squibb Pharmaceuticals Limited and Pfizer Limited

30th January 2012

Response to the Appraisal Consultation Document: Rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation

Approved Name of Medicinal Product:	Rivaroxaban
Brand Name:	Xarelto
Company:	Bayer/Johnson & Johnson

Bristol-Myers Squibb Pharmaceuticals Ltd. and Pfizer Ltd. welcome the opportunity to review and comment on the Appraisal Consultation Document (ACD) relating to the ongoing appraisal of rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation (AF).

BMS/Pfizer believe that patients with atrial fibrillation should have access to all efficacious medicines in the UK. However, we have some concerns about the basis of the Appraisal Committee's (AC) conclusions relating to the appraisal of rivaroxaban. In summary:

1. We note the higher rate of GI bleeding in ROCKET-AF and suggest rivaroxaban is not recommended in patients at higher risk of bleeding
2. We are concerned that the ROCKET-AF trial is not generalisable to the UK primary care population with AF, and suggest that rivaroxaban is restricted to a secondary care AF patient population
3. We are surprised that no conclusions were drawn from the clinical or cost-effectiveness comparison with dabigatran etexilate, and ask the Appraisal Committee to outline its reasoning

We therefore ask the Appraisal Committee to take these comments into account in its reconsideration of its preliminary recommendation.

Detailed Comments in ACD

Our detailed comments on the ACD and Evaluation Report are structured under the four questions posed by NICE in the consultation:

1. Has all of the relevant evidence been taken into account?
2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
4. Are there any aspects of the recommendations that need particular consideration to ensure that NICE avoids unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

1. Has all of the relevant evidence been taken into account?

BMS/Pfizer consider that all relevant clinical evidence has been taken into account, and we are not aware of any additional clinical or cost-effectiveness evidence that should be considered.

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Clinical evidence

Higher rate of GI bleeding in rivaroxaban patients

Although results from the as-treated population in the ROCKET-AF study indicate that rivaroxaban is superior to warfarin in preventing stroke and systemic embolism, the gastrointestinal bleeding rate was significantly higher for the rivaroxaban cohort than for warfarin (3.15% vs 2.16%; $p<0.001$), as reported in the Supplementary Appendix of the main trial paper [Patel et al, 2009]. In light of this important safety concern, we would suggest that consideration is given to not recommending the use of rivaroxaban in patients at high risk of bleeding.

ROCKET-AF population not generalisable to primary care

The average risk of stroke, as measured by the $CHADS_2$ stroke risk tool in randomised patients in ROCKET-AF, was 3.5, and only 0.2% of the trial population had a $CHADS_2$ score of 0 or 1. Patients with AF presenting in UK primary care settings frequently have a $CHADS_2$ score between 0 to 2 [Gallagher et el, 2008; Mant et al, 2007], and therefore a lower risk of stroke. This implies that the results based on the ROCKET-AF trial population cannot be generalised with confidence to all AF patients managed in UK general practice, and suggests that rivaroxaban should be recommended only for patients at higher risk of stroke, consistent with the trial population.

Mean TTR of ROCKET-AF population was low at only 55%

The mean time in therapeutic range (TTR) for the warfarin arm of the ROCKET-AF study was 55%, which the clinical experts consulted by the Appraisal Committee agreed was at the low end of the range expected in UK clinical practice. We agree with the Appraisal Committee that this could under-estimate the effectiveness of warfarin in real-life UK clinical practice. This raises further questions over the generalisability of the ROCKET-AF results to patients with AF in the UK.

Baseline imbalance of myocardial infarction in ROCKET-AF

Despite randomisation, the number of patients with a history of prior myocardial infarction (MI) at baseline was significantly higher for the warfarin arm of ROCKET-AF (18.0% vs 16.6%; $p<0.05$). The trial publication reports 0.9% rate of MI in the rivaroxaban group and 1.1% in the warfarin group (HR 0.81, 95% CI 0.63, 1.06; $p=0.121$). However, the higher baseline MI rate in the warfarin group calls into question the validity of this apparent numerical advantage for rivaroxaban on the MI secondary endpoint.

Exploratory network meta-analysis
The ERG undertook a new, exploratory network meta-analysis (NMA) to reduce the degree of heterogeneity in the network. Three studies of warfarin versus aspirin were included, stating that 'comparable dosing strategies were included.' However, the aspirin studies selected all used 300mg/day doses, while the licensed UK dosing for aspirin is 75-300mg/day (NICE CG36, p.65). Furthermore, an additional selection criterion was studies utilising a 'target INR range between 2 and 3' (the recommended UK range for VKA anti-thrombotic therapy in AF (NICE CG36, p.65). However, one of the studies included in the new NMA, SPAF2, had a target INR range of 2-4.5. It is therefore unclear whether the new NMA is entirely relevant to UK clinical practice.

Safety on treatment population used for secondary endpoint analysis
The secondary efficacy outcomes in ROCKET-AF were presented for the as-treated safety population, not the ITT population as is usual for clinical efficacy. The ACD states (pp.18-19) that the clinical specialists considered the trial ITT population to be the gold standard for estimating clinical effectiveness in a superiority trial but, since ROCKET-AF was a non-inferiority trial, the primary analysis was different. The Appraisal Committee considered that the ITT population included people who had either had no treatment or switched treatment during the trial, and concluded that the estimates derived from the safety-on-treatment population of the ROCKET-AF trial provided an adequate basis for evaluating clinical effectiveness.

However, non-inferiority trials are required to consider both ITT and per-protocol populations as equally important in determining whether non-inferiority has been met [Lesaffre, 2008: p.154], a view endorsed by the EU regulatory agency [EMEA, 2000: p.6; Schumi & Wittes, 2011: p.4]. Furthermore, when considering superiority in a non-inferiority trial, this is acceptable from a statistical perspective provided the ITT population is given the most weight (EMEA 2000, p.6; Lesaffre 2008, p.154). The ROCKET-AF trial tested for non-inferiority and superiority on the ITT (all randomised patients) in addition to the on-treatment populations (Patel et al, 2011, p.885). Therefore, it is unclear why the Appraisal Committee have concluded that the on-treatment population (all ITT patients who received at least one dose of study drug and were followed-up for events, NICE rivaroxaban ACD, p.18) is the more appropriate analysis for consideration of primary and secondary efficacy outcomes in this instance. This conclusion appears to be incorrect, and BMS/Pfizer request that the Appraisal Committee reconsider this and use the ITT data for the clinical efficacy outcomes as the base case in the rivaroxaban submission.

Comparison with dabigatran etexilate
While BMS/Pfizer concede that the Appraisal Committee's conclusion that clinical effectiveness estimates from the network meta-analyses for rivaroxaban compared with dabigatran etexilate and aspirin may be unreliable, we are surprised that the Committee further concludes that it will not consider this comparison further. Could the Appraisal Committee provide an explanation of the reasoning behind this decision, and how it intends to consider the relative cost-effectiveness of rivaroxaban compared to dabigatran etexilate and aspirin?

3. The provisional recommendations are a sound and suitable basis for guidance to the NHS

BMS/Pfizer consider the provisional recommendations set out in the ACD are not a sound basis for guidance to the NHS.

BMS/Pfizer advocate that patients with AF should have access to all efficacious medicines and note that the ROCKET-AF trial suggests that rivaroxaban is superior to warfarin in the prevention of stroke and systemic embolism. However, BMS/Pfizer note the higher rates of gastro-intestinal bleeding with rivaroxaban and would therefore suggest that patients at high risk of bleeding are specifically excluded from any recommendation by NICE.

In addition, given the considerable questions over the generalisability of ROCKET-AF to a primary care population with AF, we suggest that the most appropriate recommendation for rivaroxaban may be for patients with atrial fibrillation who are being managed in a hospital clinic.

4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

BMS/Pfizer do not consider there are any aspects of the recommendations that need particular consideration regarding unlawful discrimination against any group.

References

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