**Cardiovascular Subcommittee of PTAC**

**Meeting held 27 February 2014**

**(minutes for web publishing)**

Cardiovascular Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

Note that this document is not necessarily a complete record of the Cardiovascular Subcommittee meeting; only the relevant portions of the minutes relating to Cardiovascular Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Cardiovascular Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes were reviewed by PTAC at its meeting on 8 & 9 May, the record of which will be available in July 2014.

**Record of the Cardiovascular Subcommittee of PTAC meeting**

**held on 27 February 2014**

### Ranolazine

#### Discussion

The Subcommittee noted its previous recommendation that an additional treatment for refractory angina should be funded and that nicorandil had subsequently been listed on the Pharmaceutical Schedule as a result of this recommendation. However it considered that there may be a niche role for ranolazine in patients in particular populations who have refractory angina that is unresponsive to perhexiline or nicorandil. These particular populations include diabetics. The Subcommittee predicted that there would be approximately 100 patients within this patient group.

#### Recommendation

The Subcommittee **recommended** that ranolazine be listed in Section B and in Part II of Section H of the Pharmaceutical Schedule with a high priority restricted to patients with angina for whom either perhexiline or nicorandil has failed.

### Rivaroxaban for stroke prevention in atrial fibrillation

#### Application

The Subcommittee reviewed an application from Bayer for the listing of rivaroxaban (Xarelto) on the Hospital Medicines List (HML, Part II of Section H of the Pharmaceutical Schedule) and in Section B of the Pharmaceutical Schedule for stroke or systemic embolism prevention in atrial fibrillation (AF).

#### Recommendation

The Subcommittee recommended that rivaroxaban be funded with a medium priority for stroke or systemic embolism prevention in AF.

The Subcommittee considered that there was no clinical reason to list rivaroxaban with a Special Authority restriction, given dabigatran is listed without restriction currently.

The Decision Criteria particularly relevant to this decision are: 1) The health needs of all eligible people within New Zealand; 3) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; 4) The clinical benefits and risks of pharmaceuticals; and 5) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health & disability support services.

#### Discussion

The Subcommittee noted that PTAC at its meeting in November 2012 had deferred making a recommendation for rivaroxaban in AF pending review by the

Neurological, Haematology, and Cardiovascular Subcommittees. The Subcommittee noted that the Neurological and Haematology Subcommittees had both given rivaroxaban positive recommendations for funding in this indication, medium and low priority recommendations respectively.

The Subcommittee considered that the key evidence for rivaroxaban was the ROCKET-AF trial (Patel et al. N Engl J Med. 2011;365:883-91). The Subcommittee noted that it was a double-blind randomised controlled trial and the trial design had selected a higher risk patient population with worse CHADS2 scores when compared to the trials for dabigatran and apixaban.

The Subcommittee considered that ROCKET-AF, while only one trial, was of excellent quality and good strength. The Subcommittee noted that in the intention-to-treat (ITT) analysis, rivaroxaban was not superior to warfarin for the primary endpoint of stroke or systemic embolism (2.1% versus 2.4% respectively, HR 0.88 (95% CI 0.75-1.03) p=0.12 for superiority). The Subcommittee noted that rivaroxaban had similar major bleeding rates to warfarin (3.6% versus 3.4% respectively, HR 1.04 (95% CI 0.90-1.20), p=0.58). Rivaroxaban was associated with significantly lower rates of intracranial haemorrhage (0.5% versus 0.7%, HR 0.67 (95%CI 0.47-0.93, p=0.02) but higher rates of gastrointestinal bleeding (3.2% versus 2.2%, p<0.001).

The Subcommittee noted that unlike dabigatran, the pivotal trial reported that rivaroxaban was not associated with higher rates of myocardial infarction (0.9% versus 1.1% respectively, HR 0.81 (95% CI 0.63-1.06, p=0.12); therefore, rivaroxaban may be preferred for patients at a higher risk of myocardial infarctions. The Subcommittee noted that although there may be a difference in rates of myocardial infarction between dabigatran and rivaroxaban, the difference may not be clinically significant. The Subcommittee noted that the ROCKET-AF study excluded patients with a creatinine clearance <30mL/min and although rivaroxaban was not predominantly excreted through the kidneys, it would be inappropriate to conclude that rivaroxaban could be used in patients with a creatinine clearance <30mL/min.

The Subcommittee considered that rivaroxaban was not significantly better than warfarin in terms of efficacy and was similar to warfarin in terms of bleeding risk. The Subcommittee considered that overall, rivaroxaban did not appear more efficacious than dabigatran (150mg twice daily dose) although it noted that there was no head-to-head trial comparing these two agents. The Subcommittee noted that although rivaroxaban has a similar plasma-half-life profile to dabigatran and apixaban, it is a once-daily treatment, meaning missing a dose of rivaroxaban could have more adverse effects.

The Subcommittee noted than unlike dabigatran, rivaroxaban could be blister-packed. The Subcommittee noted that there is currently no good evidence to confirm that any one of these new oral anticoagulants is easier to reverse than the others. The Subcommittee noted that a Factor Xa reversal agent is currently being developed.

The Subcommittee considered that the patient group most likely to benefit from rivaroxaban was potentially those with labile international normalised ratios

(INRs) who cannot tolerate dabigatran or have a previous history of myocardial infarction.

The Subcommittee considered that, since warfarin and dabigatran were both open-listed, there was no clinical reason to place a Special Authority restriction on rivaroxaban. The Subcommittee considered that it would be beneficial to have a Factor Xa inhibitor funded and based on the available clinical evidence on the efficacy and safety of apixaban and rivaroxaban, it would prefer apixaban over rivaroxaban. The Subcommittee considered that there were no safety concerns with having more than one of these novel oral anticoagulants listed.

**Apixaban for stroke prevention in atrial fibrillation**

**Application**

The Subcommittee reviewed an application from Pfizer for the listing of apixaban (Eliquis) on the Hospital Medicines List (HML, Part II of Section H of the Pharmaceutical Schedule) and in Section B of the Pharmaceutical Schedule for stroke or systemic embolism prevention in atrial fibrillation (AF).

**Recommendation**

The Subcommittee recommended that apixaban be funded with a high priority for stroke or systemic embolism prevention in AF.

The Subcommittee considered that there was no clinical reason to list apixaban with a Special Authority restriction given dabigatran is listed without restriction currently.

The Decision Criteria particularly relevant to this decision are: 1) The health needs of all eligible people within New Zealand; 3) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; 4) The clinical benefits and risks of pharmaceuticals; and 5) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health & disability support services.

**Discussion**

The Subcommittee noted that this funding application had not yet been reviewed by PTAC. The Subcommittee noted that the Neurological and Haematology Subcommittees had both given apixaban positive recommendations for funding in this indication, medium and high priority recommendations respectively.

The Subcommittee considered that the evidence for apixaban were the ARISTOTLE trial (N Engl Med. 2001; 365-981-92) and the AVERROES trial (N Engl Med. 2011;364:806-17). The Subcommittee noted the results from those studies. The Subcommittee considered that the clinical studies were of excellent quality. The Subcommittee noted that the ARISTOTLE study reported that when compared to warfarin, apixaban was associated with lower rates of stroke and lower rates of bleeding. The Subcommittee noted that there was also a trend indicating that with increasing patient age, apixaban was safer than warfarin in terms of major bleeding rates.

The Subcommittee noted that although there was no head-to-head study, the available evidence indicate that apixaban is associated with lower rates of major bleeding when compared to dabigatran (Dentali. Circulation 2012; 126: 2381-2391). When comparing the ROCKET-AF and ARISTOTLE studies, the Subcommittee considered that apixaban was associated with lower rates of stroke and bleeding when compared to rivaroxaban. The Subcommittee considered that this observation concorded with the venous thromboembolism (VTE) treatment studies for apixaban and rivaroxaban (Agnelli et al. N Engl J Med 2013:369:799-808; EINSTEIN Investigators. N Engl J Med 2010;363:2499-2510). The Subcommittee noted that apixaban had bleeding rates similar to those of patients on aspirin.

The Subcommittee considered that there is currently no good evidence to confirm that any one of these new oral anticoagulants is easier to reverse than the others.

The Subcommittee noted that the ARISTOTLE study excluded patients with a creatinine clearance of <25ml/min and the medicine is not primarily renally-cleared. The Subcommittee considered that it would be helpful if the supplier could provide further information on the outcomes of the subset of patients with a creatinine clearance between 25 and 29ml/min included in the trial.

The Subcommittee considered that the patients most likely to benefit from apixaban would be:

1.1.1 Patients with labile international normalised ratios (INRs) who cannot tolerate dabigatran;

1.1.2 Patients at higher risk of bleeding;

1.1.3 Patients with renal impairment; and

1.1.4 Patients with a body weight of less than 60kg.

The Subcommittee considered that, since warfarin and dabigatran were both open-listed, there was no clinical reason to place a Special Authority restriction on apixaban. The Subcommittee considered that it would be beneficial to have a Factor Xa inhibitor funded and based on the available clinical evidence on the efficacy and safety of apixaban and rivaroxaban, it would prefer apixaban over rivaroxaban. The Subcommittee considered that there were no safety concerns with having more than one of these novel oral anticoagulants listed.