Haematology Subcommittee of PTAC
Meeting held 16 March 2016

(minutes for web publishing)

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

The Haematology 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 5 & 6 May 2016, a record of which will be available in due course.

1 Matters arising

Idarucizumab funding application

1.1 The Subcommittee noted that PTAC had reviewed an application from Boehringer Ingelheim for the funding of idarucizumab (Praxbind) in DHB hospitals for dabigatran reversal. Members noted that PTAC recommended that idarucizumab be listed on the HML for the specific reversal of the anticoagulant effects of dabigatran, in situations of life-threatening or uncontrolled bleeding, or for emergency surgery or urgent procedures, with a medium priority.

1.2 The Subcommittee reviewed the interim analysis by Pollack et al. (N Engl J Med. 2015;373:511- 20) of the first 90 patients in the RE-VERSE AD phase-III multinational prospective open-label interventional case series. The Subcommittee noted RE-VERSE AD's primary end point is the reversal of anticoagulant effect determined by dilute thrombin time (dTT) and ecarin clotting time (ECT), which are surrogate markers of clinical efficacy.

1.3 The Subcommittee considered that idarucizumab was effective at reversing dabigatran and was clinically necessary for those patients with either life-threatening bleeding or for emergency surgery or urgent procedures. The Subcommittee considered the majority of cases of severe bleeding on dabigatran were associated with patients who had deterioration in renal function.

1.4 The Subcommittee noted a draft guidance document for idarucizumab developed by clinicians from Auckland District Health Board (ADHB). The Subcommittee noted that the suggested dose was 2.5 g, which is half the dose used in the RE-VERSE AD study.

1.5 The Subcommittee noted the ADHB guidance document suggested idarucizumab should be restricted to situations where there is a documented evidence of dabigatran effect (TCT > 80 seconds or aPTT > 40 seconds) or if critical surgery is required with an admission to theatre time of < 60 minutes. The Subcommittee considered it would be a rare occurrence for the use of idarucizumab to be clinically justified in advance of the baseline coagulation studies becoming available. The Subcommittee considered that in most situations there would be an expectation that the bleeding would require radiological confirmation, which would allow sufficient time for urgent blood results to be obtained.

1.6 The Subcommittee considered that the number of patients who truly needed a dabigatran reversal agent was very small. The Subcommittee considered that if funding for idarucizumab was approved, it would be difficult to restrict usage and clinicians would likely err on the side of using it rather than not using it. If funded, the Subcommittee strongly recommended an audit of practice.

1.7 The Subcommittee **recommended** that restrictions to approve the administration of idarucizumab might include approval by appropriately qualified specific senior clinicians such as emergency medicine or intensive care specialists, consultant anaesthetists or haematologists, although noted rostered cover for this would be difficult, especially in small hospitals.

1.8 The Subcommittee considered that it was difficult to determine if the reversal agent would save lives, given the variability of each case. The Subcommittee considered the health benefits from dabigatran reversal with idarucizumab were difficult to quantify given the lack of comparator arm in the RE-VERSE AD study. The Subcommittee considered there may be health benefits of dabigatran reversal if treatment is provided early for presentations of intracranial or spinal haemorrhage, severe gastrointestinal bleeding with haemodynamic instability and other major life-threatening trauma. The Subcommittee considered the number (of cases) need to treat (NNT) to prevent a death may be high, but is not able to be quantified based on the available evidence.

1.9 The Subcommittee considered there is also insufficient data on improved health outcomes for warfarin reversal in life-threating situations such as intracranial haemorrhage. Members further considered that in the event of the successful treatment of an intracranial bleed, the likelihood of the patient still experiencing functioning debilitation was high, but this could not be predicted in advance of a decision to treat.

1.10 The Subcommittee **recommended** that the listing of idarucizumab on the HML be accompanied by a robust audit process to monitor use and outcomes.

2 New haemophilia treatments – update

2.1 The Subcommittee noted a paper by PHARMAC staff requesting updated clinical advice on potential future haemophilia treatments, specifically on long-acting recombinant factor VIII (rFVIII) and factor IX (rFIX) products, as trial data on Biogen's long-acting treatments has now been published subsequent to the Subcommittee's previous discussion in 2013 on these treatments.

2.2 The Subcommittee considered that there are approximately 600 patients in New Zealand with haemophilia, and 150-200 would be considered to have severe haemophilia. These patients have regular bleeds unless on prophylaxis. The Subcommittee noted that haemophilia A is approximately four times more common than haemophilia B.

2.3 The Subcommittee considered there are different regimens for prophylaxis, and the aim is to reduce bleed frequency by maintaining a trough factor activity of ≥1%. Members considered the number of bleeds varies, even within the severe group, dependent on patient factors and the presence of target joints and comorbidities.

2.4 The Subcommittee noted the results of 'A-LONG' (Mahlangu el al. Blood. 2014;123:317-25) a Phase III open-label study which reported a 1.5-fold increase in the terminal factor VIII half-life for rFVIIIFc compared to rFVIII (19 hours versus 12.4 hours, $p<0.001$). Members noted for the individualized therapy group, the factor VIII weekly dose was approximately 80iu/kg. [Withheld].

2.5 The Subcommittee noted the interim results of 'ASPIRE' (Nolan et al. Haemophilia. 2016;22:72-80) a Phase III open-label trial following on from the A-LONG and from the Kids A-LONG trials. The Subcommittee considered this trial confirms the long-term efficacy and safety of rFVIIIFc.

2.6 The Subcommittee noted the results of 'B-LONG' (Powell et al. N Engl J Med. 2013;369:2313-23) a Phase III open-label study which reported a 2.43-fold increase in the terminal factor IX half-life for rFIXFc compared to rFIX (82.12 versus 33.77 hours

respectively; p<0.001). Members noted that in the latter part of the study, greater than 50% (53.8%) of study subjects in group 2, treated with interval-adjusted rFIXFc prophylaxis commencing at 100 IU per kilogram every 10 days, achieved dosing intervals ≥ 2 weeks.

2.7 The Subcommittee noted a post-hoc analysis by Powell et al (Br J Haematol. 2015 Jan;168:113-23) reported 30–50% reductions in weekly FIX consumption, reduced infusion frequency, a greater likelihood of maintaining FIX activity >1% and fewer bleeding episodes compared with prior FIX prophylaxis.

2.8 The Subcommittee noted a second post-hoc analysis by Powell et al (Br J Haematol. 2015;168:124-34) reported effective haemostasis during major surgery. Compared to a population pharmacokinetic model there was no shortening of the rFIXFc half-life in the perioperative setting.

2.9 The Subcommittee noted the results of 'Kids A-LONG' (Young G et al. J Thromb Haemost. 2015;13:967-77) a phase III open-label study evaluating the safety, efficacy and pharmacokinetics of a longer-acting factor, recombinant factor VIII Fc fusion protein (rFVIIIFc), in previously treated children with severe haemophilia A. Members noted subjects receiving a pre-study FVIII regimen of three intravenous infusions per week experienced an approximately 33% reduction in annual infusions with twice-weekly rFVIIIFc prophylaxis.

2.10 The Subcommittee considered that the pharmacokinetics were different in each patient which would result in variable drug half-life durations, especially in children. The Subcommittee considered that pharmacokinetic testing would need to be conducted in each patient to ensure adequate prophylaxis rates and appropriate dosing. Members noted that small daily doses of the currently available short acting preparations are excellent at providing prophylaxis and if patients were willing to submit to 3-doses per week they would spend more time over 3% factor activity, which would be likely to result in an annual bleeding rate near zero. Regular infusions are however less convenient.

2.11 The Subcommittee considered there was still insufficient evidence to support a reduction in annualised bleeding rates with the longer-acting treatments; however there was a benefit to patients from a reduced injection frequency. The Subcommittee noted there were no results available from previously untreated patients (PUP) studies. The Subcommittee considered these would need to be available before the long-acting treatments would be used in newly diagnosed children.

2.12 [withheld] The Subcommittee considered that group most likely to benefit from long-acting treatments would be paediatric patients with haemophilia B, as the number of injections required for the long-acting agents are significantly less than the short-acting agents. Members considered the burden of care for the family and caregivers of paediatric haemophilia patients would be reduced considerably through reductions in injection frequency. The Subcommittee considered that intravenous injections were often difficult for both the child and any family members involved, and this may have adverse health effects on those individuals.

2.13 The Subcommittee noted that current practice in New Zealand for haemophilia involves early prophylaxis in newly diagnosed children, usually starting after a joint or muscle bleed and always after a significant bleed such as an intracranial bleed. The

Subcommittee considered that venous access to provide such treatment is distressing for both the child and parent and may impact on regimen adherence, and that, in infants and young children, difficulties with venous access necessitates an intravenous device such as a port.

2.14 The Subcommittee considered the availability of longer-acting agents could result in a small number of patients with poor venous access or adherence difficulties being more amenable to prophylactic treatment instead of their current on-demand treatment. The Subcommittee considered that almost all patients who need prophylaxis are currently accessing this treatment.

2.15 Members considered that if the long-acting agents were funded, without restrictions, all children would commence on treatment with long-acting treatments, provided the PUP studies demonstrate no additional risk of inhibitor development.

3 NOAC commercial options

3.1 The Subcommittee considered a paper by PHARMAC staff seeking clinical advice on potential future funding options for novel oral anticoagulants (NOACs).

3.2 The Subcommittee noted that there are no head-to-head studies comparing rivaroxaban, apixaban and dabigatran; however there had been a number of published network meta-analyses indirectly comparing the efficacy and adverse event profiles of dabigatran, apixaban, and rivaroxaban. The Subcommittee considered that based on the available evidence, dabigatran, apixaban, and rivaroxaban have the same or similar therapeutic efficacy, with similar risks.

3.3 The Subcommittee considered that if only one NOAC was to be funded, apixaban would be preferred over rivaroxaban based on the evidence for slightly lower bleeding rates with equivalent efficacy. The Subcommittee considered that both factor Xa inhibitors would be preferred over dabigatran, primarily due to lower renal clearance and reduced gastrointestinal adverse effects.

3.4 The Subcommittee noted an indirect comparison by Kang and Sobieraj (Thromb Res 2014;133:1145-51) of the NOACs, including rivaroxaban, apixaban, dabigatran and edoxaban, for the treatment of acute venous thromboembolism (VTE). Members considered that the although differences in mortality or VTE recurrence between NOACs were observed, there was a statistically significant increase in major bleeding in patients taking dabigatran compared with apixaban [RR 2.69 (1.19 to 6.07)]. No significant differences were found amongst other comparisons. The Subcommittee noted there was a trend in the direction of increased risk of major bleeding with rivaroxaban compared to apixaban, but this did not reach statistical significance.

3.5 The Subcommittee noted a fixed-effect network analysis by van der Hulle et al (J Thromb Haemost 2014; 12: 320-8) making an indirect comparison between rivaroxaban, dabigatran, apixaban, and edoxaban, which reported no difference in mortality or VTE recurrence between rivaroxaban and the other NOACs.

3.6 The Subcommittee noted that a descriptive study by Agnelli et al (N Engl J Med 2013: 369: 799-808) reported that apixaban was associated with significantly lower rates of

bleeding (major or clinically relevant) when compared with warfarin, 4.3% versus 9.7% respectively (RR 0.44, p<0.001).

3.7 The Subcommittee noted that although dabigatran was also associated with less bleeding overall when compared with warfarin (5.6% versus 8.8% respectively, hazard ratio, 0.63, p=0.002), the occurrence of gastrointestinal bleeding with dabigatran was almost twice that observed with warfarin (Schulman et al. N Engl J Med 2009; 361(24): 2342-52).

3.8 The Subcommittee noted a network meta-analysis by Dogliotti et al (Heart. 2014 Mar;100:396-405) comparing anticoagulants in non-valvular atrial fibrillation. The Committee noted that there were no significant differences reported between the NOACs and warfarin in effects on stroke, systemic embolism, mortality or major bleeding, although the point estimates favoured the NOACs over warfarin. The Subcommittee noted no difference when dabigatran was compared with apixaban and rivaroxaban. In terms of overall bleeding, the Committee noted that there was no reported difference in combined major bleeding between the NOACs and vitamin K antagonists.

3.9 The Subcommittee noted the ROCKET-AF trial (Patel et al. N Engl J Med. 2011;365:883-91) for rivaroxaban had selected a higher risk patient population with worse CHADS2 scores when compared with the trials for dabigatran and apixaban.

3.10 The Subcommittee noted that a descriptive study by Culebras et al (Neurology 2014; 82:716-24) reported increased gastrointestinal bleeding with rivaroxaban and dabigatran when compared with apixaban, but less intracranial bleeding for all the NOACs when compared with vitamin K antagonists. The Subcommittee considered the overall difference in bleeding rates were small and unlikely to be clinically significant.

3.11 The Subcommittee noted a PHARMAC retrospective descriptive analysis of dabigatran usage from prescription claims data for the period of 1 July 2011 through to 30 June 2014. The Subcommittee noted the median discontinuation time was 61 weeks overall, but for those that discontinued treatment with dabigatran the median period of treatment was 3.3 months, with almost half of these patients moving to warfarin or aspirin.

3.12 The Subcommittee considered that dabigatran had the highest rate of gastrointestinal adverse effects amongst the NOACs, with reportedly 12-15% of trial participants discontinuing dabigatran for that reason. Members considered, based on their own clinical experience, that the rate of gastrointestinal discomfort associated with dabigatran is likely to be significantly higher than this, and may lead to poor adherence in a number of patients.

3.13 The Subcommittee noted that renal clearance was much higher with dabigatran (80%) than with rivaroxaban (~30%) and apixaban (25-30%). The Committee considered this is a potential disadvantage for dabigatran, as renal impairment is common in the patient group requiring anticoagulant treatment. Members considered that deterioration in renal function has been associated with the majority of the significant bleeding events in patients taking dabigatran.

3.14 The Subcommittee considered that dabigatran capsules needed to be swallowed whole, and cannot be blister packed. Members considered that it would preferable to have a funded NOAC which is blister packed.

3.15 The Subcommittee noted the correspondence to PTAC from a clinical pharmacist who considered that rivaroxaban should be the preferred NOAC due to adherence advantages of once daily dosing.. The Committee considered that although once-daily dosing provides an advantage for rivaroxaban, its half-life is shorter than dabigatran and apixaban. The Subcommittee noted potential management difficulties in the elderly or those with cognitive impairment, which increases the potential consequences of missing a dose.

3.16 The Subcommittee noted European Heart Rhythm Association guidance (Heidbuchel et al. Europace. 2013;15:625–651) that suggests an alternative NOAC can be initiated when the next dose is due, except in situations where higher-than therapeutic plasma concentrations are expected (e.g. in a patient with impaired renal function). The Subcommittee noted that this guidance is also supported by the US Label information for the NOACs.

3.17 The Subcommittee considered that a switch from one NOAC to another would not be clinically unreasonable. The Subcommittee further considered that funding one NOAC would be reasonable if, for the majority of patients, the NOAC was well tolerated, and with a second NOAC being available for the group of patients who could not tolerate the associated side effects. .

3.18 The Subcommittee considered that, based on data obtained at the conclusion of the NOAC clinical trials, there is evidence to suggest that switching between NOAC's and warfarin carries an increased risk of thrombotic events, but switching between the NOACs does not appear to carry this same risk.

3.19 The Subcommittee considered that it would be clinically reasonable to implement a switch of both new and existing patients to a factor Xa inhibitor being the solely funded NOAC. The Subcommittee considered education materials for clinicians in both primary and secondary care settings would be necessary if a change was proposed.

3.20 The Subcommittee noted that while there was an antidote for dabigatran registered in New Zealand, there was currently no available antidote for factor Xa inhibitors, but this may be available in the future. The Subcommittee considered that the availability of an antidote was an advantage, but does not outweigh the potential advantages of listing a factor Xa inhibitor, given that the lower renal clearance of the factor Xa inhibitors may result in a lower need for an antidote.