# Haematology Subcommittee of PTAC
# Meeting held 22 November 2013

## (minutes for web publishing)

Haematology 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 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 13 &14 February 2014, the record of which will be available in May 2014.

# Record of the Haematology Subcommittee of PTAC meeting held at PHARMAC on 22 November 2013

## 1 Summary of recommendations

The Subcommittee recommended that:

1.1 The criteria for rituximab in ITP as initially consulted on be amended;

1.2 The criteria for rituximab in TTP initially consulted on be amended;

1.3 Access to rituximab in hospitals be widened to include PRCA;

1.4 The access criteria for eltrombopag be amended;

1.5 PHARMAC seek feedback from transfusion specialists and anaesthetists before making changes to the access to erythropoietin in hospitals;

1.6 Members of this Subcommittee review the guidelines for dabigatran when used perioperatively and in the setting of bleeding;

1.7 Tinzaparin is not listed on the HML and that PHARMAC assist the DHB currently using tinzaparin in its transition from tinzaparin to the other listed low molecular weight heparins;

1.8 Apixaban be listed on the HML and in Section B of the Pharmaceutical Schedule for VTE only if it was cost-neutral to enoxaparin, dabigatran and rivaroxaban;

1.9 Apixaban be listed on the HML and in Section B of the Pharmaceutical Schedule for patients with AF with a high priority;

1.10 Rivaroxaban be funded with a high priority for the treatment of VTE but excluding patients who develop VTE in the setting of malignancy;

1.11 Rivaroxaban be funded with a medium priority for the secondary prevention of VTE; and

1.12 Rivaroxaban be funded with a low priority for stroke and systemic embolism prevention in AF.

## 2 Matters arising and correspondence

### *2.1 Rituximab in various haematology indications*

2.1.1 The Subcommittee considered the responses received following PHARMAC's consultation to widen funded access to rituximab in hospitals to include certain haematology indications.

2.1.2 The Subcommittee considered that based on the feedback received and the clinical evidence, it would be appropriate to enable patients with Idiopathic Thrombocytopenic Purpura (ITP) who have platelet counts in the range of 20 to 30 X $10^9$/L to receive funded rituximab if they also have significant mucocutaneous bleeding. The Subcommittee also noted that platelet count readings could vary depending on the laboratory test used. The Subcommittee considered that it would be appropriate to maintain the requirement that patients would only be considered for funded rituximab retreatment for ITP if they have had a response lasting at least 12 months to prior rituximab treatment, which reflects current New Zealand practice.

2.1.3 The Subcommittee considered that splenectomy remains an effective treatment in ITP with studies showing a sustained response rate of approximately 70%-80% (Neunert et al. Blood 2011; 117(16): 4190). The Subcommittee considered that rituximab is an effective treatment but is associated with lower response rates (62.5%) and less durable responses (durable response at 1 year of 30%) (Neunert et al. Blood 2011; 117(16): 4190) compared with splenectomy. The Subcommittee noted the recommendations from two sets of guidelines, the American (Neunert et al. Blood 2011; 117(16): 4190) and British (British Journal of Haematology 2003; 120: 574) guidelines in relation to ITP. The Subcommittee considered that the American guidelines were more up to date and that the guidelines considered that there was grade 1B evidence supporting the efficacy of splenectomy for patients who have failed corticosteroid therapy. The American guidelines also recommend that rituximab (grade 2C evidence) may be considered for patients at risk of bleeding who have failed one line of therapy such as corticosteroids, intravenous immunoglobulin (IVIg) or splenectomy.

2.1.4 The Subcommittee noted that there are also significant side effects associated with rituximab therapy and its long term safety where repeated use in ITP is unknown (Arnold et al. Ann Intern Med 2007; 146: 25-33). The Subcommittee also noted that although splenectomy is associated with risks, its safety has improved with good immunisation protocols and antimicrobial prophylaxis. Therefore, the Subcommittee considered that it would be appropriate that splenectomy is used ahead of rituximab in ITP treatment algorithms. The Subcommittee noted that one of the criteria consulted on, 'splenectomy is an absolute contraindication', could be subjective. However, the Subcommittee considered that it was difficult to further define the criterion and it should be left unchanged. The Subcommittee noted that an audit of prescribing could be done if rituximab use in this setting increased significantly beyond what would be expected.

2.1.5 The Subcommittee **recommended** that the criteria for rituximab in ITP as initially consulted on be amended as follows (additions in bold):

Initiation – immune thrombocytopenic purpura - haematologist
*Limited to 4 weeks' treatment*
Both:

**1. Either:**
- 1.1. Patient has immune thrombocytopenic purpura with a platelet count of ≤ 20,000 platelets per microlitre; or
- 1.2. **Patient has immune thrombocytopenic purpura with a platelet count of 20,000 to 30,000 platelets per microliter and significant mucocutaneous bleeding;** and

2. Any of the following:
- 2.1. Treatment with steroids and splenectomy have been ineffective; or
- 2.2. Treatment with steroids has been ineffective and splenectomy is an absolute contraindication; or
- 2.3. Other treatments including steroids have been ineffective and patient is being prepared for elective surgery (e.g. splenectomy).

Continuation – immune thrombocytopenic purpura - haematologist
*Limited to 4 weeks' treatment*
Either:

1. Previous treatment with lower doses of rituximab (100 mg weekly for 4 weeks) have proven ineffective and treatment with higher doses (375 mg/$m^2$ weekly for 4 weeks) is now planned; or
2. All of the following:
   - 2.1 Patient was previously treated with rituximab for immune thrombocytopenic purpura; and
   - 2.2 An initial response lasting at least 12 months was demonstrated; and
   - 2.3 Patient now requires repeat treatment.

2.1.6 The Subcommittee noted the consultation feedback in regards to funding of rituximab for Thrombotic Thrombocytopenic Purpura (TTP). The Subcommittee noted the feedback that the 'clinical response to plasma exchange was suboptimal or plasma exchange is contraindicated' criterion was too vague and it should instead be based on the British guidelines (Scully et al. British Journal of Haematology 2012; 158: 323-335). The Subcommittee considered that it would be appropriate to define disease refractory to plasma exchange as progression of clinical symptoms or persistent thrombocytopenia despite plasma exchange. The Subcommittee also noted that the British guidelines also recommended that rituximab is used in conjunction with plasma exchange in patients with acute idiopathic TTP with neurological or cardiac pathology which are associated with a high mortality. The Subcommittee considered that it would be appropriate to allow rituximab to be funded for use with plasma exchange in this patient group and this reflects current New Zealand clinical practice. The Subcommittee **recommended** that the criteria for rituximab in TTP initially consulted on be amended as follows (changes in strikethrough, additions in bold):

Initiation – thrombotic thrombocytopenic purpura - haematologist
~~Both:~~
**Either:**

1. Patient has thrombotic thrombocytopenic purpura **and has experienced progression of clinical symptoms or persistent thrombocytopenia despite plasma exchange**; **or**
2. **Patient has acute idiopathic thrombotic thrombocytopenic purpura with neurological/cardiovascular pathology.**
   ~~Clinical response to plasma exchange was suboptimal or plasma exchange is contraindicated~~.

Continuation – thrombotic thrombocytopenic purpura - haematologist
All of the following:
1. Patient was previously treated with rituximab for thrombotic thrombocytopenic purpura; and
2. An initial response lasting at least 12 months was demonstrated; and
3. Patient now requires repeat treatment.

2.1.7 The Subcommittee noted that PHARMAC had received feedback during consultation that rituximab is also used in DHB hospitals to treat pure red cell aplasia (PRCA). The Subcommittee considered that this reflected current New Zealand clinical practice and would be clinically appropriate, although funding for this indication was not consulted on. The Subcommittee considered that PRCA was often associated with chronic lymphocytic leukaemia (CLL) and rituximab treatment resulted in high response rates of >80% (Michallet et al. Leukaemia and Lymphoma 2011; 52(7): 1401-1403). The Subcommittee considered that the patient numbers accessing funded rituximab for PRCA would be very small. The Subcommittee **recommended** that access to rituximab in hospitals be widened to include PRCA as follows:

**Initiation – pure red cell aplasia** - haematologist
*Limited to 6 weeks' treatment*
Patient has autoimmune pure red cell aplasia associated with a demonstrable B-cell lymphoproliferative disorder.

**Continuation – pure red cell aplasia** - haematologist
*Limited to 6 weeks' treatment*
Patient was previously treated with rituximab for pure red cell aplasia associated with a demonstrable B-cell lymphoproliferative disorder and demonstrated an initial response lasting at least 12 months.

*2.2 <u>Eltrombopag in idiopathic thrombocytopenic purpura</u>*

2.2.1 The Subcommittee noted the responses received following PHARMAC's consultation on a proposal to list eltrombopag for ITP. The Subcommittee noted that some respondents had requested that rituximab become a treatment option in patients who had not responded to two immunosuppressive therapies after a trial of two months each, rather than the proposed period of three months each. The Subcommittee considered that a trial period of three months each is appropriate. The Subcommittee also noted that a respondent had suggested that eltrombopag be funded for ITP for use concurrently with other first and second-line immunosuppressive therapies, instead of intravenous immunoglobulin (IVIg), to support patients temporarily whilst waiting for those immunosuppressive therapies to work. The Subcommittee considered that there is currently no

clinical evidence to support the use of eltrombopag in this setting and the proposed treatment strategy would make it difficult to determine which treatment was having an effect as well as present a fiscal risk.

2.2.2 The Subcommittee noted that a respondent had asked if steroids were regarded as a 'line of therapy' in ITP and the Subcommittee considered that they were. A respondent also asked if dependence on an unacceptably high steroid dose was considered 'failing' a line of therapy. The Subcommittee considered that an unacceptably high steroid dose was not considered 'failing' a line of therapy because the disease was responding to the steroid therapy. The Subcommittee considered that including a criterion to allow eltrombopag to be used if patients have experienced unacceptable toxicities from other treatments would present a fiscal risk given the subjective nature of the criterion. Therefore, the Subcommittee considered that it would be appropriate to not include such a criterion and instead consider these patients through the Named Patient Pharmaceutical Assessment (NPPA) process. The Subcommittee considered that it would review this issue if it becomes apparent after the listing of eltrombopag that the access criteria require modification. The Subcommittee considered that it would be appropriate to allow eltrombopag to be used in patients who have platelet counts between 20,000 and 30,000 platelets per microliter if they also have significant mucocutaneous bleeding. The Subcommittee noted that this would reflect current clinical guidelines and would be consistent with the access changes proposed by the Subcommittee for rituximab in ITP. The Subcommittee considered that this proposed change would not result in a significant fiscal risk as the patient numbers would be small, about 5 extra patients per year. The Subcommittee **recommended** that the access criteria for eltrombopag be amended as follows (deletions in strikethrough, additions in bold):

> Initial application - (idiopathic thrombocytopenic purpura – post-splenectomy) only from a haematologist. Approvals valid for 6 weeks for applications meeting the following criteria:
> All of the following:
> 1. Patient has had a splenectomy; and
> 2. Two immunosuppressive therapies have been trialled and failed after therapy of 3 months each (or 1 month for rituximab); and
> 3. ~~Either~~ **Any of the following**:
>    3.1. **Patient has a platelet count of 20,000 to 30,000 platelets per microliter and has evidence of significant mucocutaneous bleeding; or**
>    3.2. Patient has a platelet count of ≤20,000 platelets per microlitre and has evidence of active bleeding; or
>    3.3. Patient has a platelet count of ≤10,000 platelets per microlitre.
>
> Initial application - (idiopathic thrombocytopenic purpura – preparation for splenectomy) only from a haematologist. Approvals valid for 6 weeks where the patient requires eltrombopag treatment as preparation for splenectomy.
>
> Renewal– (idiopathic thrombocytopenic purpura – post-splenectomy) from a haematologist. Approvals valid for 12 months where the patient has obtained a response (see Note) from treatment during the initial approval or subsequent renewal periods and further treatment is required.

Note: Response to treatment is defined as a platelet count of >30,000 platelets per microlitre.

*2.3* *Imatinib brand switch*

2.3.1 The Subcommittee noted that PHARMAC recently consulted on a proposal to award sole supply status for imatinib for non-gastrointestinal stromal tumour (non-GIST) indications. The Subcommittee noted that the proposal would involve a brand switch for non-GIST patients from Glivec to Imatinib-AFT. It would also involve the cessation of direct distribution of imatinib to non-GIST patients. The Subcommittee noted the proposed implementation plan including communications to patients, haematologists, general practitioners and pharmacists. The Subcommittee did not have concerns with the proposal.

## 3 Tinzaparin

### Application

3.1 The Subcommittee reviewed an application from a clinician for the inclusion of tinzaparin on the Hospital Medicines List (HML, Part II of Section H of the Pharmaceutical Schedule).

### Recommendation

3.2 The Subcommittee **recommended** that tinzaparin is not listed on the HML. The Subcommittee **recommended** that PHARMAC assist the DHB currently using tinzaparin in its transition from tinzaparin to the other listed low molecular weight heparins.

### Discussion

3.3 The Subcommittee noted that this application was received as a response to PHARMAC's decision to exclude tinzaparin from the Hospital Medicines List (HML, Part II of Section H of the Pharmaceutical Schedule) at its inception on 1 July 2013. The Subcommittee noted that tinzaparin is used widely in one DHB, as an alternative to enoxaparin or dalteparin which are currently listed on the Pharmaceutical Schedule. The Subcommittee noted that no other DHB used (prior to 1 July 2013) or currently uses tinzaparin. The Subcommittee noted that the applicant states that tinzaparin is preferred over other low molecular weight heparins (LMWHs) because it is the only LMWH that has prospectively-collected data on pharmacokinetic, safety and efficacy end points to support its use as a once-daily treatment during pregnancy. The Subcommittee noted that the DHB has protocols in place for the use of tinzaparin and it has been used there for many years.

3.4 The Subcommittee noted the clinical evidence provided in the submission. The Subcommittee considered that the majority of evidence for tinzaparin in pregnancy was Level 3 evidence. The Subcommittee noted that there is variation in the registered dosing schedules of these agents due to variations in how the

relevant pivotal clinical trials were done. However, the Subcommittee noted that, although there is clinical trial evidence to support once-daily dosing of tinzaparin (unlike the other LMWHs), the pharmacokinetic profiles of all LMWHs were very similar.

3.5 The Subcommittee noted that the available published guidelines do not single out tinzaparin as being superior to the other LMWHs in clinical situations including pregnancy. The Subcommittee considered that all LMWHs are accepted to have similar efficacy regardless of what treatment was used in a particular clinical trial. The Subcommittee noted that in clinical practice, enoxaparin is often prescribed once daily in pregnancy.

3.6 The Subcommittee considered that if tinzaparin was listed on the HML, it could be used in other DHBs as well as the DHB currently using it. The Subcommittee considered that this would present a safety risk as all the LMWHs have different dosing regimens and there is very little clinical experience with tinzaparin amongst clinicians and nursing staff in other DHBs. This is also a concern given junior clinicians rotate through different hospitals.

3.7 Overall, the Subcommittee considered that there was insufficient evidence to support a benefit of tinzaparin over the other available treatment options and that there would be safety concerns with listing tinzaparin on the HML. The Subcommittee noted that if tinzaparin was not listed on the HML, the DHB would need to put in place new treatment protocols and implement a planned transition to one of the listed treatment options.

## 4 Apixaban in venous thromboembolism prophylaxis following major orthopaedic surgery and stroke prevention in atrial fibrillation

### Application

4.1 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 venous thromboembolism (VTE) prophylaxis following major orthopaedic surgery and stroke prevention in atrial fibrillation (AF). The Subcommittee noted that this funding application has not yet been reviewed by the Pharmacology and Therapeutics Advisory Committee (PTAC).

### Recommendations

4.2 The Subcommittee considered that there was no clinical reason not to list apixaban for VTE prophylaxis following major orthopaedic surgery and **recommended** that it be listed on the HML and in Section B of the Pharmaceutical Schedule for VTE only if it was cost-neutral to enoxaparin, dabigatran and rivaroxaban.

4.3 The Subcommittee **recommended** that apixaban be listed on the HML and in Section B of the Pharmaceutical Schedule for patients with AF with a high priority.

4.4 The Subcommittee considered that there was no clinical reason to list apixaban with a Special Authority restriction given dabigatran is listed without restriction currently; however, it would be reasonable to place a restriction on its use for the various indications based on cost, in order to allow the recommendations to be progressed independently.

4.5 **The Decision Criteria particularly relevant to this recommendation are:** ***(i) The*** *health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; and (iv) The clinical benefits and risks of pharmaceuticals; (vi) The budgetary impact of any changes to the Pharmaceutical Schedule and (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

**Discussion**

4.6 *VTE prophylaxis following major orthopaedic surgery*

4.6.1 The Subcommittee noted that rivaroxaban, dabigatran and enoxaparin are currently funded treatments for VTE prophylaxis following major orthopaedic surgery.

4.6.2 The Subcommittee considered that the evidence for apixaban, a Factor Xa inhibitor in this indication was of good quality. The Subcommittee noted the results from the ADVANCE 1 (Lassen et al. N Engl J Med. 2009; 361(6): 594-604), ADVANCE 2 (Lassen et al. Lancet. 2010: 375(9717): 807-15) and ADVANCE 3 (Lassen et al. N Engl J Med. 2010; 363(26): 2487-2498) trials. The Subcommittee noted that there was a high drop-out rate (around 30%) in the ADVANCE trials. The Subcommittee noted that the available clinical evidence supports that apixaban is at least as effective as enoxaparin for VTE prophylaxis following major orthopaedic surgery. The Subcommittee also noted that there were mild liver function tests abnormalities but no signal of increased myocardial infarction risks with apixaban when compared to enoxaparin. The Subcommittee noted that the available clinical evidence suggests that bleeding risks is also lower with apixaban when compared to enoxaparin.

4.6.3 The Subcommittee also noted the clinical evidence for rivaroxaban and dabigatran in this indication. The Subcommittee considered that apixaban, dabigatran and rivaroxaban had similar efficacy in VTE prophylaxis following major orthopaedic surgery, based on indirect comparisons.

4.6.4 The Subcommittee noted that there is variable use of anticoagulation pharmaceuticals by orthopaedic surgeons due to concerns about bleeding risks. The Subcommittee considered that, based on the currently available clinical evidence, there is insufficient evidence to confirm that any of the new oral anticoagulants (apixaban, dabigatran, rivaroxaban) is safer than the other in the

clinical scenario where anticoagulation needs to be reversed. The Subcommittee considered that apixaban was potentially associated with a lower risk of bleeding when compared to rivaroxaban or dabigatran based on indirect comparisons of those treatments with enoxaparin. The Subcommittee noted that, unlike dabigatran, apixaban is not largely renally excreted and is, therefore, safer in patients with renal impairment. However, the Subcommittee noted that rivaroxaban, which is also not largely renally excreted, is currently available funded for use in patients with renal impairment.

4.7 *Stroke prevention in AF*

4.7.1 The Subcommittee noted that the Neurological Subcommittee of PTAC had reviewed this application at its meeting in September 2013. The Subcommittee noted the draft minutes from the Neurological Subcommittee meeting and noted that it had recommended that apixaban be funded with medium priority, restricted by Special Authority to patients with AF and renal impairment with a creatinine clearance of <30 ml/min.

4.7.2 The Subcommittee noted that dabigatran and warfarin are currently funded treatments for patients with AF.

4.7.3 The Subcommittee considered that the clinical evidence for apixaban in stroke prevention in AF was of good quality (Granger et al. N Engl J Med 2011; 365: 981-92 and (Connolly et al. N Engl J Med 2011: 364: 806-17). The Subcommittee reviewed the clinical evidence for dabigatran and rivaroxaban in this indication (Connolly et al. N Engl J Med 2009; 361: 1139-51 and Patel MR et al. N Engl J Med 2011; 365(10): 883-91). The Subcommittee considered that the available evidence indicated that apixaban had similar efficacy to warfarin and dabigatran. Based on an indirect comparison of the evidence, the Subcommittee noted that apixaban appeared slightly more efficacious than rivaroxaban. The Subcommittee also noted that apixaban was associated with a lower risk of bleeding when compared to warfarin and likely also dabigatran and rivaroxaban when indirectly compared. The Subcommittee noted that apixaban was not associated with an increased risk of myocardial infarction when compared to warfarin, unlike dabigatran. The Subcommittee noted that apixaban was also associated with fewer upper gastrointestinal tract side effects than dabigatran.

4.7.4 The Subcommittee considered that the patient group most likely to benefit from apixaban was patients with AF who could not tolerate warfarin or dabigatran, have an increased bleeding risk or who have poor renal function. The Subcommittee considered that if apixaban was funded, the size of the market would grow as there would be more treatment options for patients who require anticoagulation.

4.7.5 The Subcommittee considered that there were safety concerns with having more than one of these novel oral anticoagulants listed given the different dosing regimens and risk of inadvertent switching between the different agents. The Subcommittee considered that apixaban has clinical advantages over currently available treatment options in that it is associated with less bleeding, is safer in patients with renal impairment and is associated with less gastrointestinal side effects. However, the Subcommittee noted that cost, and cost-effectiveness,

should be taken into account when considering which of these new oral anticoagulants to fund. The Subcommittee considered that if more than one of these newer agents are funded, consideration would need to be given to developing national guidelines to guide prescribing and mitigate some of the safety concerns.

## 5 Rivaroxaban in venous thromboembolism treatment, secondary prevention and stroke or systemic embolism prevention in atrial fibrillation

### Application

5.1 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 venous thromboembolism (VTE) treatment, VTE secondary prevention and stroke or systemic embolism prevention in atrial fibrillation (AF).

### Recommendations

5.2 The Subcommittee **recommended** that rivaroxaban be funded with a high priority for the treatment of VTE but excluding patients who develop VTE in the setting of malignancy.

5.3 The Subcommittee **recommended** that rivaroxaban be funded with a medium priority for the secondary prevention of VTE.

5.4 The Subcommittee **recommended** that rivaroxaban be funded with a low priority for stroke and systemic embolism prevention in AF.

5.5 The Subcommittee considered that there was no clinical reason to list rivaroxaban with a Special Authority restriction given dabigatran is listed without restriction currently; however, it would be reasonable to place a restriction on its use for the various indications based on cost, in order to allow the recommendations to be progressed independently.

5.6 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iv) The clinical benefits and risks of pharmaceuticals; (vii) The direct cost to health service users and (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

### Discussion

5.7 *VTE treatment*

5.7.1 The Subcommittee noted that PTAC had reviewed this funding application for rivaroxaban in VTE treatment at its meeting in November 2012 and had deferred

making a recommendation until it was reviewed by the Haematology Subcommittee. The Subcommittee noted that current funded treatments for VTE treatment are: (1) bridging enoxaparin followed by warfarin and (2) enoxaparin (for patients with malignancies or who are pregnant). The Subcommittee noted that dabigatran is currently being evaluated by Medsafe for VTE treatment and its registration for this indication is expected in early 2014.

5.7.2 The Subcommittee noted that the management of VTE is changing towards hospital-independent treatment with the availability of these new oral treatments. The Subcommittee considered that deep vein thromboses (DVT) and pulmonary emboli (PE) have the same disease process and patients with DVTs often have occult PEs.

5.7.3 The Subcommittee reviewed the evidence for rivaroxaban, a Factor Xa inhibitor, in the treatment of VTE. The Subcommittee also reviewed the evidence for a direct thrombin inhibitor (dabigatran) and other Factor Xa inhibitors (apixaban and edoxaban) for the treatment of VTE. The Subcommittee considered that, overall, these agents are not inferior to warfarin in the prevention of recurrent VTEs. However, the Subcommittee noted that there was no significant difference in the rates of major or clinically relevant bleeding between rivaroxaban and warfarin (EINSTEIN Investigators. N Engl J Med 2010; 363: 2499-2510). The Subcommittee noted that apixaban was associated with significantly lower rates of bleeding (major or clinically relevant) when compared to warfarin, 4.3% versus 9.7% respectively, RR 0.44, $p<0.001$) (Agnelli et al. N Engl J Med 2013: 369: 799-808). The Subcommittee noted that although dabigatran was associated with less bleeding overall when compared to warfarin (5.6% versus 8.8% respectively, HR 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).

5.7.4 The Subcommittee noted that rivaroxaban did not result in net clinical benefit when compared to warfarin in the EINSTEIN-PE study (3.4% versus 4.0% respectively, HR 0.85, $p=0.28$). The Subcommittee noted that rivaroxaban is taken once daily, unlike dabigatran and apixaban, although its half-life is shorter than dabigatran or apixaban. The Subcommittee considered that there is potentially a greater risk of VTE recurrence with rivaroxaban if a dose is missed.

5.7.5 The Subcommittee considered that, overall, the evidence for rivaroxaban in the treatment of VTE is of good quality and strength. The Subcommittee considered that, if funded, rivaroxaban would be preferred over warfarin and enoxaparin because it is an oral treatment which does not require frequent monitoring. The Subcommittee also considered that the Factor Xa inhibitors would be favoured over dabigatran because dabigatran is associated with a greater risk of gastrointestinal bleeding and is not appropriate in patients with renal impairment. There is also a concern of increased acute coronary syndrome risk with dabigatran. The Subcommittee considered that there is insufficient evidence currently to confirm if any one of Factor Xa inhibitors is easier to reverse than the others in the event of bleeding, but the Factor Xa inhibitors are possibly easier to reverse than dabigatran.

5.7.6 The Subcommittee considered that the Factor Xa inhibitors should not currently be used to treat VTE in the setting of malignancy due to the absence of evidence in this patient group. The Subcommittee noted that there were safety concerns with having more than one of these novel oral anticoagulants listed given the different dosing regimens and risk of inadvertent switching between the different agents. The Subcommittee considered that cost and cost-effectiveness should be taken into account when considering which of these new oral anticoagulants to fund. The Subcommittee considered that if more than one of these newer agents was funded, consideration would need to be given to developing national guidelines to guide prescribing and mitigate some of the safety concerns.

5.8 *Venous thromboembolism secondary prevention*

5.8.1 The Subcommittee noted that PTAC had reviewed this funding application for rivaroxaban in VTE secondary prevention at its meeting in November 2012 and had deferred making a recommendation until it was reviewed by the Haematology Subcommittee. The Subcommittee noted that current funded treatment options in this indication are warfarin and aspirin (the latter for lower-risk populations). The Subcommittee noted the clinical evidence for rivaroxaban, apixaban and dabigatran in the secondary prevention of VTE. The Subcommittee noted that there was a net clinical benefit (composite VTE and major bleeding rates) associated with rivaroxaban when compared to placebo (2.0% versus 7.1% respectively, HR 0.28, p<0.001) (EINSTEIN Investigators. N Engl J Med 2010; 363: 2499-2510). The Subcommittee noted that there were similar outcomes for apixaban and dabigatran versus placebo (Agnelli et al. N Engl J Med 2013; 368:699-708 and Schulman et al. N Engl J Med 2013; 368:709-718).

5.8.2 The Subcommittee noted that only dabigatran has been trialled head-to-head against warfarin in this indication (Schulman et al. N Engl J Med 2013; 368:709-718). The Subcommittee noted that in terms of the rate of recurrent VTE, dabigatran was not inferior to warfarin (1.8% versus 1.3% respectively, HR 1.44; 95% CI 0.78 to 2.64; p=0.01 for non-inferiority). However, the Subcommittee noted that acute coronary syndromes occurred more frequently in those treated with dabigatran (0.9%) versus warfarin (0.2%) (P=0.02). The Subcommittee noted that apixaban was associated with lower bleeding rates, more similar to aspirin than the other new agents.

5.8.3 The Subcommittee noted that because there are no head-to-head trials of rivaroxaban versus warfarin or aspirin, there is no evidence to confirm that rivaroxaban is more efficacious than current available treatments in the secondary prevention of VTE.

5.9 *Prevention of stroke and systemic embolism in atrial fibrillation*

5.9.1 The Subcommittee noted that the Neurological Subcommittee of PTAC had reviewed the funding application for rivaroxaban in stroke prevention in AF at its meeting in September 2013. The Subcommittee noted that the Neurological Subcommittee had recommended that rivaroxaban be funded with medium priority restricted by Special Authority to patients with AF and renal impairment with a creatinine clearance of <30 ml/min.

5.9.2 The Subcommittee reviewed the clinical evidence for rivaroxaban, apixaban and dabigatran in this indication. The Subcommittee noted that, unlike dabigatran, rivaroxaban does not significantly reduce the risk of ischaemic stroke when compared to warfarin (Patel et al. N Engl J Med 2011; 365:883-891). Rivaroxaban was also associated with higher bleeding rates versus warfarin (3.6% and 3.4% respectively; P=0.58) although this was not statistically significant.

5.9.3 The Subcommittee noted that the study for rivaroxaban in AF is a double-blind randomised controlled trial whilst that for dabigatran was an open-label study. The Subcommittee noted that the international normalised ratio (INR) monitoring time in treatment range (TTR) for those in the warfarin arm was also lower in the rivaroxaban study (55%) versus other studies (62%-75%) (Patel et al. N Engl J Med 2011; 365:883-891). The Subcommittee noted that this could have biased the trial results in favour of rivaroxaban. The Subcommittee also noted that there were higher rates of stroke or systemic embolism in the rivaroxaban arm versus warfarin arm after cessation of randomised treatment. The Subcommittee had concerns about whether the once daily dosing for rivaroxaban is supported by the pharmacological data.

5.9.4 The Subcommittee considered that, based on indirect comparisons, it is possible that that rivaroxaban is therapeutically equivalent to dabigatran.

## 6 Overview of haemophilia treatments

6.1 The Subcommittee reviewed a memorandum from PHARMAC staff on haemophilia treatments.

6.2 The Subcommittee noted that PHARMAC had made a decision to include the funding of certain haemophilia treatments – the recombinant blood factors and FEIBA (Factor Eight Inhibitor Bypassing Fraction) – into the Combined Pharmaceuticals Budget. The Subcommittee also noted that subsidy and delisting protection for the currently funded products ends on 30 June 2014, as per the terms of the last Request for Proposals (RFP).

6.3 The Subcommittee noted that there are new treatments currently undergoing registration in other countries or in late stages of trial development, namely the longer-acting recombinant Factor VIIIs and IXs. The Subcommittee noted that PHARMAC staff were seeking the Subcommittee's preliminary view on these longer-acting treatments to help inform the next RFP process for the haemophilia treatments. The Subcommittee noted that PHARMAC will also be seeking the advice of the National Haemophilia Management Group (NHMG) and the Haemophilia Treaters Group (HTG) on this matter.

6.4 The Subcommittee noted that in New Zealand, a majority of children with haemophilia who require treatment are on a prophylactic regimen whereas adults are mainly on an on-demand regimen. The Subcommittee noted that there are approximately 600 patients with haemophilia in New Zealand and 150-200 patients have severe haemophilia. The Subcommittee noted that

approximately 25% of patients are children and 80% of patients with severe haemophilia would have regular bleeds if not on prophylaxis treatment.

6.5 The Subcommittee noted that bleeding patterns for patients with haemophilia can vary, as well as the response to treatments for those bleeds. The Subcommittee advised that most treatments are self-administered by patients at home with the oversight of their treating centres. Patients are provided with guidelines on how much product should be used depending on the type of bleed. Very few patients require hospitalisation for their bleeds. The Subcommittee considered that the dosing regimens outlined in the datasheets for the various recombinant factors VIII and IX reflected current practice in New Zealand.

6.6 The Subcommittee noted that there are national guidelines on the management of haemophilia but considered that these need to be updated. The Subcommittee noted that the care of haemophilia patients involves a multidisciplinary team, including physiotherapists, nurses and doctors. The Subcommittee noted that with the availability of current treatments, the life expectancy of patients with severe haemophilia is approaching that of the normal population, although their quality of life may be reduced. Before the availability of any treatment, patients with haemophilia had a life expectancy of approximately 20 years.

6.7 The Subcommittee noted that Biogen Idec had longer-acting recombinant factors in development and that these factors could be registered in New Zealand as early as the end of 2014 or early 2015. Members noted that, on PHARMAC's request, Biogen Idec had provided some preliminary trial data on its new longer-acting Factor VIII and IX. The Subcommittee noted the results from the A-LONG study, a Phase III study of Biogen Idec's long-lasting recombinant factor VIII Fc fusion protein (rFVIIIFc) in patients with severe haemophilia A (Mahlangu et al. Blood. Pre-published November 13, 2013; 10.1182/blood-2013-10-52997). The Subcommittee noted that the A-LONG study excluded children ≤ 12 years old but a trial in children is ongoing (Kids A-LONG). The Subcommittee noted that the annualised bleeding rates were reduced in patients treated with rFVIIIFc in all arms except those who continued on episodic treatment. The Subcommittee noted that the terminal half-life of rFVIIIFc was extended by 1.5-fold when compared to rFVIII (19 hours versus 12.4 hours, $p<0.001$). The Subcommittee also noted that no subjects developed inhibitors although the Subcommittee noted that the group of patients included in the trial were at low risk of developing inhibitors anyway.

6.8 The Subcommittee noted the preliminary results from the B-LONG study, a Phase III study of long-lasting recombinant factor IX Fc fusion protein (rFIXFc) in patients with severe haemophilia B (unpublished preliminary trial data provided by supplier in poster and slide forms). This study also excluded children aged ≤ 12 years old. The trial results indicate that there was a 2.43-fold increase in the terminal factor IX half-life for rFIXFc compared to rFIX when a 96-hour sampling schedule was used (82.12 versus 33.77 hours respectively; $p<0.001$). The Subcommittee noted that approximately 50% of subjects in Arm 2 of the study (individualised prophylaxis cohort) achieved dosing intervals ≥ 2 weeks.

6.9 The Subcommittee considered that the evidence so far indicates that these newer longer-acting factors are effective and likely to be safe. The Subcommittee noted that the prolonged half-lives would mean that patients would require less frequent intravenous injections which could improve quality of life through increased compliance. The Subcommittee noted that in the A-LONG study, almost two thirds of patients still required dosing two to three times per week. The Subcommittee noted that the advance provided by rFIXFc is more clinically significant than that provided by rFVIIIFc. Patients with haemophilia B are already dosing once weekly, hence an increase to dosing intervals ≥ 2 weeks would further improve convenience and compliance.

6.10 The Subcommittee considered that these treatments would benefit patients on prophylaxis regimens but would be limited to adult patients until the trials in children are completed. The Subcommittee also noted that the availability of these longer-acting agents would result in more patients being amenable to prophylactic treatment and, therefore, more patients gaining the benefits of fewer bleeding episodes.

6.11 The Subcommittee considered that these new treatments would likely be preferred over current treatments when used prophylactically for new patients, although new patients are children and there is currently no clinical evidence to support the efficacy and safety of these new agents in children. The Subcommittee considered that many existing adult patients on prophylactic regimens would be switched to these new agents but it would be unlikely that all would switch if they are stable on current treatments.

6.12 The Subcommittee considered that it would need to review funding applications for these new longer-acting factors before providing final recommendations to PHARMAC.