Haematology Subcommittee of PTAC
Meeting held 30 January 2019

(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 will be reviewed at the May 2019 meeting of PTAC.

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1 Matters Arising and Correspondence

Correspondence from HFNZ

1.4 The Subcommittee noted correspondence from the Haemophilia Foundation of New Zealand (HFNZ) dated 18 July 2018 and 20 November 2018 regarding the Subcommittee's previous minutes relevant to extended half-life haemophilia treatments.

1.5 The Subcommittee noted HFNZ strongly support the availability of extended half-life treatment funding for all patients with haemophilia in New Zealand. HFNZ also considered equal prioritisation be given to extended half-life rFVIII and rFIX and that the therapeutic differences should be considered when assessing RFPs. The Subcommittee noted HFNZ's views were expressed as being independent of industry.

1.6 The Subcommittee noted HFNZ support the availability of emicizumab and would like to see this therapy funded in the near future.

1.7 The Subcommittee thanked HFNZ for the correspondence and noted PHARMAC had, on 29 January 2019, released a consultation on a proposal for changes to funded haemophilia treatments. This consultation included proposed funding of both an extended half-life rFVIII and rFIX option. The Subcommittee noted additional detail on PHARMAC's analysis of the proposals received in the haemophilia RFP and a funding application for emicizumab for haemophilia A with inhibitors was on the agenda for discussion at this meeting.

2 Emicizumab for haemophilia A with inhibitors

Application

2.4 The Subcommittee considered a funding application from Roche Products (New Zealand) Ltd for emicizumab for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.

2.5 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

2.6 The Subcommittee **recommended** that emicizumab be funded with a high priority for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors due to high unmet need, high cost of current treatments and the suitability of subcutaneous treatment.

2.7 The Subcommittee **recommended** emicizumab be funded subject to the following Special Authority criteria:

> Initial application only from a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has severe congenital haemophilia A and history of bleeding and bypassing agent usage within the last six months, with either:

1.1. Greater than or equal to 6 documented and treated spontaneous bleeds within the last 6 months if on an on-demand bypassing agent regimen; or
1.2. Greater than or equal to 2 documented and treated spontaneous bleeds within the last 6 months if on a bypassing agent prophylaxis regimen;

2. Patient has a high-titre inhibitor to Factor VIII (greater than or equal to 5 Bethesda units per mL), which has persisted for six months or more;
3. There is no immediate plan for major surgery within the next 12 months;
4. The patient has either failed immune tolerance induction (ITI) after an initial period of 12 months, or the Haemophilia Treaters Group considers the patient is not a suitable candidate for ITI; and
5. Treatment is to be administered at a maximum of dose of 3 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly.

Renewal only from a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:

1. No more than two spontaneous and clinically significant treated bleeds after the end of the loading dose period i.e. after the first four weeks of treatment until the end of the 24-week treatment period; and
2. The treatment remains appropriate and the patient is benefiting from treatment.

Discussion

2.8 The Subcommittee noted that haemophilia A is a hereditary, life-long bleeding disorder due to deficiency of coagulation factor VIII (FVIII) which results in prolonged spontaneous and injury-related bleeding, progressive joint damage and potentially life-threatening bleeds. The Subcommittee noted that patients with haemophilia A can develop FVIII inhibitors (antibodies) from exposure to FVIII replacements over time which render FVIII therapy ineffective, and that persistent FVIII inhibitors lead to worse quality of life, joint damage and poor outcomes.

2.9 The Subcommittee noted that haemophilia A affects approximately 1 in 5000 live male births and there are currently approximately 500 patients with haemophilia A in New Zealand; of these, approximately 135 patients have severe disease (defined as less than 1% of the normal level of FVIII and a strong tendency to spontaneously bleed). The Subcommittee noted approximately 25% of patients with severe haemophilia and 5% of patients with mild-moderate haemophilia develop inhibitors to FVIII, with only a small number of those with severe haemophilia and persistent inhibitors requiring Immune Tolerance Induction (ITI) or treatment with bypassing agents.

2.10 The Subcommittee considered that there is a high burden for families of patients with haemophilia A, especially if the patient is a young child, due to difficult intravenous (IV) treatment administration of replacement FVIII several times a week and the impact of the disease on schooling, work and lifestyle for the patient and family members.

2.11 The Subcommittee noted that patients with haemophilia A and an inhibitor to FVIII largely require on-demand treatment for bleeding events, surgery or as secondary prophylaxis following a bleeding event. The standard treatment in these instances is bypassing agents, primarily factor eight inhibitor bypassing fraction (FEIBA NF) or occasionally recombinant factor VIIa (NovoSeven RT). The Subcommittee noted that FEIBA NF and NovoSeven RT require frequent IV infusions that are difficult in children due to access, otherwise these treatments can be administered using an implanted venous access device such as a Port-A-Cath which carries additional risks (e.g. risk of infection or port-associated thrombosis).

2.12 The Subcommittee noted bypassing agent prophylaxis with FEIBA NF is not current practice in New Zealand primarily due to cost, although there are instances of its use.

2.13 The Subcommittee considered that successful inhibitor neutralisation can provide the best outcomes for patients with haemophilia A with FVIII inhibitors and the current standard approach for this is ITI consisting of frequent (usually daily) high-dose FVIII treatments commencing soon after development of FVIII inhibitors. The Subcommittee noted that ITI is an intensive and expensive treatment usually administered in children for 24 months (with a review after 12 months), which has a 70% success rate, but has some risks associated with IV treatment and a high treatment burden for patients and families.

2.14 The Subcommittee considered that a child with haemophilia A with inhibitors would be considered for ITI promptly and may not meet the proposed Special Authority criteria proposed for emicizumab in this application due to a lack of sufficient bleeding history. The Subcommittee noted that the evidence currently available is for patients who have a bleeding history.

2.15 The Subcommittee noted that patients with severe haemophilia A usually develop inhibitors within their first 50 days of exposure to exogenous FVIII and there are currently approximately 15 patients in New Zealand who have severe haemophilia A with high-titre inhibitors (defined as ≥5 Bethesda units per mL) based on current bypassing agent usage data.

2.16 The Subcommittee noted the results of the HAVEN 1 trial, a randomised, phase III, multi-centre, open-label trial which investigated the efficacy and safety of subcutaneous (SC) emicizumab prophylaxis administered once-weekly compared with no prophylaxis in 109 male patients with haemophilia A with FVIII inhibitors who were 12 years of age or older (Oldenburg et al. N Engl J Med. 2017;377:809-18).

2.17 The Subcommittee noted the HAVEN 1 trial annualised bleed rate was 2.9 events (95% CI, 1.7 to 5.0) with emicizumab prophylaxis versus 23.3 events (95% CI, 12.3 to 43.9) with no prophylaxis (P<0.001), and that 63% of patients on emicizumab prophylaxis had zero bleeds. The Subcommittee considered that although the HAVEN 1 trial had relatively small patient numbers, that emicizumab prophylaxis was highly effective in reducing bleed rate.

2.18 The Subcommittee noted the increased risk of life-threatening thrombotic microangiopathy due to concurrent FEIBA administration in patients receiving emicizumab prophylaxis in the HAVEN 1 trial. The Subcommittee considered that it would be difficult to manage patients undergoing major surgery whilst on emicizumab, and there is little experience currently with managing bypassing agents during this time but significant quantities of NovoSeven RT are likely to be required.

2.19 The Subcommittee noted the interim results of the HAVEN 2 trial, a non-randomised, phase III, multi-centre, open-label trial which investigated the efficacy, safety and pharmacokinetics of SC emicizumab prophylaxis administered in paediatric (<12 years) patients with haemophilia A with inhibitors (F Hoffman-La Roche Ltd, Interim CSR Study BH29992, Report No. 1083442, March 2018 [unpublished]). The Subcommittee noted that the trial design included three cohorts; Cohort A (once-weekly emicizumab, n=68), Cohort B (two-weekly emicizumab, n=10) and Cohort C (four-weekly emicizumab, n=10) and at the time of the interim analysis (data cut-off date 05 October 2017), efficacy data was available for 59 patients in Cohort A only.

2.20 The Subcommittee noted the results of the HAVEN 2 trial primary analysis (data cut-off date 30 April 2018), presented at the American Society of Haematology (ASH) conference in 2018. The annualised bleed rate for patients ages <12 years in Cohorts A, B and C were 0.3 (95% CI 0.17-0.50), 0.2 (0.03-1.72) and 2.2 (0.69-6.81) respectively for treated bleeds. The Subcommittee noted zero treated bleeds were reported in 50/65 (76.9%), 9/10 (90%) and 6/10 (60%) of patients in Cohorts A, B and C respectively (G Young et al. Emicizumab Prophylaxis Provides Flexible and Effective Bleed Control in Children with Hemophilia A with Inhibitors: Results from the HAVEN 2 Study. Presented at ASH 2018).

2.21 The Subcommittee noted that anti-drug antibodies (ADA) were detected in three HAVEN 2 trial participants, which impacted on the function of emicizumab for one patient. The Subcommittee considered it was unclear whether the development of ADA was related to duration of treatment on emicizumab.

2.22 The Subcommittee considered that the HAVEN 2 trial provided good evidence and included reasonable patient numbers for this difficult to study patient group, and that randomisation or blinding would not have been feasible.

2.23 The Subcommittee considered that emicizumab is a highly effective and relatively safe treatment which prevents bleeds in a large proportion of patients with haemophilia A with FVIII inhibitors.

2.24 The Subcommittee considered that emicizumab is a suitable agent for the treatment of haemophilia A for patients with inhibitors due to the once-weekly subcutaneous administration, low level of administration-related risk and low hospital resource use for a disease which heavily utilises the health system.

2.25 The Subcommittee considered that emicizumab should be listed for haemophilia A patients with inhibitors who have severe disease, but noted defining a group was challenging and there would be pressure to use in patients with less severe disease also. The Subcommittee considered that this subgroup would receive the most benefit from emicizumab prophylaxis due to high morbidity, high need and otherwise poor treatment options.

2.26 Members noted the criteria proposed by the Subcommittee includes a specific number of bleeds prior to starting and this could be difficult for clinicians, especially given that identifying a spontaneous bleed can be challenging.

2.27 The Subcommittee considered that clarification was needed regarding the optimal strategy for ITI and its place in the new treatment paradigm if emicizumab were to be funded considering local management and international best practice guidelines. The Subcommittee considered that emicizumab would likely be more appealing than a very intensive IV treatment despite the chances of inhibitor eradication. The Subcommittee considered that inhibitor titre decreases with treatment for some patients, but not all, and it is likely that emicizumab treatment could be lifelong if it is used in preference to ITI. The Subcommittee considered that ongoing emicizumab prophylaxis would mean that the number of patients on emicizumab would increase over time.

2.28 The Subcommittee noted that the supplier provided health economic assessment stated there would be no arthroplasty required for patients receiving emicizumab prophylaxis. The Subcommittee considered that arthroplasty would likely be required in existing patients receiving emicizumab prophylaxis due to joint damage occurring prior to commencement of emicizumab prophylaxis.

2.29 The Subcommittee considered that emicizumab prophylaxis would have benefits for hospital resource use due to fewer bleeds resulting in a reduced number of hospitalisations, reduction in associated costs such as for catheterisation, and lower hospital resource use than is required for labour-intensive IV treatment administration.

2.30 The Subcommittee considered that emicizumab is a relatively safe treatment which is effective in preventing bleeds in a large proportion of patients with haemophilia A with FVIII inhibitors and recommended that emicizumab be funded with a high priority due to high unmet need in this patient group, high cost of current treatments and the suitability of subcutaneous treatment.

3 Eltrombopag Special Authority criteria review

Application

3.4 The Subcommittee considered a paper from PHARMAC staff on the eltrombopag Special Authority criteria, noting that recent changes were made without a formal review by the Haematology Subcommittee.

3.5 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

3.6 The Subcommittee considered that the current eltrombopag criteria for 'idiopathic thrombocytopenic purpura contraindicated to splenectomy' were appropriate.

3.7 The Subcommittee **recommended** that the current initial eltrombopag criteria for 'severe aplastic anaemia' are amended as follows (bold and strikethrough), with a high priority:

> Initial application — (severe aplastic anaemia) only from a haematologist. Approvals valid for 3 months for applications meeting the following criteria:
> Both:
> 1 Two immunosuppressive therapies have been trialled and failed ~~after therapy of at least 3 months duration~~; or
> 2 Immunosuppressive therapy is contraindicated; and
> 3 Either:
> 3.1 Patient has severe aplastic anaemia with a platelet count of less than or equal to 20,000 platelets per microliter; or
> 3.2 Patient has severe aplastic anaemia with a platelet count of 20,000 to 30,000 platelets per microlitre and significant mucocutaneous bleeding.

Discussion

3.8 The Subcommittee noted eltrombopag was funded for idiopathic thrombocytopenic purpura (preparation for and post-splenectomy) from 1 January 2014. The Subcommittee noted that from 1 October 2018, access was widened to eltrombopag for idiopathic thrombocytopenic purpura contraindicated to splenectomy, and severe aplastic anaemia.

3.9 The Subcommittee noted that since April 2014, PHARMAC has received a total of 44 initial NPPA applications for eltrombopag. PHARMAC has approved 28 of the applications. The majority of applications were for patients who had refractory severe

aplastic anaemia (SAA) or refractory immune thrombocytopenic purpura (ITP) where splenectomy was contraindicated, delayed or ineffective.

Idiopathic thrombocytopenic purpura contraindicated to splenectomy

3.10 The Subcommittee recognised that the definition of "contraindicated to splenectomy" is difficult and there is potential for interpretation and higher than expected use.

3.11 The Subcommittee noted splenectomy is arguably the preferred second-line treatment option with the best long-term response rate of approximately 70%. The Subcommittee noted some clinicians prefer using rituximab second-line after corticosteroids and IVIG, but responses to rituximab are often short-lived.

3.12 The Subcommittee noted a literature review performed by PHARMAC staff located eight clinical trial publications relevant to eltrombopag and ITP since 1 January 2014.

3.13 The Subcommittee noted relevant trials including a retrospective case review based on a Spanish registry (González-López et al. Int J Hematol. 2017;106:508-16) that indicated a slightly greater efficacy in newly diagnosed patients, and two safety trials (Brynes et al. Acta Haematol. 2017;137:66-72 and Brynes et al. Am J Hematol. 2015;90:598-60) which concluded most adverse events are minor and no significant increase in bone marrow reticulin out to 5 years.

3.14 The Subcommittee noted the efficacy trials by Yang et al. (Br J Haematol. 2017;176:101-110) where 57.7% of eltrombopag-treated patients vs. 6% of placebo-treated patients achieved a platelet count > 50 x109/L at day 42, and the EXTEND trial (Wong et al. Blood. 2017;130(23):2527-2536) where 85.8% of patients achieved a platelet count ≥ 50 × 109/L at least once in the absence of rescue and 133 (52%) of 257 patients achieved a continuous response of 25 weeks or longer. The Subcommittee noted the median duration of eltrombopag treatment in EXTEND was 2.37 years (2 days-8.76 years).

3.15 The Subcommittee considered there was nothing in the updated literature which adds any concerns about the use of eltrombopag in ITP.

3.16 The Subcommittee noted the eltrombopag renewal criteria for ITP contraindicated to splenectomy require that a patient has maintained a platelet count of > 50 $x10^9$/L on treatment, whereas the post-splenectomy criteria only require a platelet count of > 30 $x10^9$/L on treatment. The Subcommittee noted the higher platelet count is consistent with the response definition used in the clinical trials and is therefore considered reasonable.

3.17 The Subcommittee noted no age restrictions are present in the criteria but eltrombopag is not yet Medsafe approved for use in children with the data sheet noting that safety and efficacy in children and adolescents has not been established. The Subcommittee noted the PETIT study (Bussel et al. Lancet Haematol. 2015;2:e315-25) in 67 patients aged 1-17 years with a platelet count < 30 $x10^9$/L and at least one prior treatment. It included age-based dosing and the Subcommittee noted responses (platelet count of > 50 x109/L) were achieved at least once in roughly 60% in all age cohorts. The Subcommittee noted the PETIT 2 study (Grainger et al. Lancet. 2015;386:1649-58) in 92 patients aged 1-17 years with a platelet count < 30 $x10^9$/L and at least one prior treatment. The Subcommittee noted 40% of eltrombopag-treated patients vs. 3% of placebo-treated patients achieved a platelet count of at least 50 × 10^9/L in the absence of rescue therapy for 6 or more weeks from weeks 5–12 of the double-blind period and 80% achieved this platelet count at least once during the open label period.

3.18 The Subcommittee considered that PETIT and PETIT 2 support similar efficacy and the adverse event profiles in adults and children of all ages, but there remains substantial uncertainly about long-term use, in particular the risk of bone marrow fibrosis. The Subcommittee also noted the lack of an oral liquid and restrictions around milk/dairy intake make dosing in small children difficult.

3.19 The Subcommittee considered the health benefit for eltrombopag comes from those for whom splenectomy is not an option with reasonably strong and robust evidence. The patient numbers will depend on how the "significant and well-documented contraindication to splenectomy for clinical reasons" is applied.

3.20 The Subcommittee discussed the requirement for two immunosuppressive therapies to have been trialled and failed after therapy of 3 months each (or 1 month for rituximab) noting that IVIG is very costly.

3.21 Members considered that widening of access to eltrombopag for short-term use in combination with immunosuppressive therapy as an interim measure until immunosuppressive therapy efficacy is observed may provide a health and cost benefit in some patients, but the Subcommittee did not conclude that a change to the criteria was appropriate.

3.22 Members considered that there are selected patients, especially elderly, where steroids are either ineffective or contraindicated, where (repeated) use of IVIG is also inappropriate or ineffective and where trialling rituximab may inappropriate. Having to wait for up to 3 months before using eltrombopag seems inappropriate in these circumstances.

Severe aplastic anaemia

3.23 The Subcommittee noted that PHARMAC had received and approved a number of eltrombopag applications under NPPA for patients with severe aplastic anaemia who have disease refractory to, or have progressed past, immunosuppressive therapy. The Subcommittee noted that to date PHARMAC has initially approved 13 weeks of eltrombopag with renewal criteria based on the trial by Olnes et al. (N Engl J Med. 2012;367:11-9).

3.24 The Subcommittee considered the unmet need with the current criteria relates to the length of time before eltrombopag can be commenced in patients in clinically unstable patients with a rapid disease trajectory where bleeding and infections are problematic. Early initiation of eltrombopag may increase the complete response rate and bring this forward in time compared to awaiting a response on immunosuppression. The Subcommittee considered it was possible that in these patients a three-month delay could be fatal or require considerable hospitalisation and other supportive health care resources including blood transfusion support.

3.25 The Subcommittee noted patient numbers that had this rapid disease trajectory would be small, likely only 1-2 patients per year.

3.26 The Subcommittee noted the evidence for adding eltrombopag to immunosuppression in severe aplastic anaemia comes from the Phase I/II study by Townsley et al. (N Engl J Med. 2017;376:1540-50) where cohort 1 received eltrombopag from day 14 to 6 months, cohort 2 from day 14 to 3 months, and cohort 3 from day 1 to 6 months. The Subcommittee noted the trial demonstrated that the longest eltrombopag exposure in cohort 3 showed the best response rate 58% compared to a 10% historical control, although patient numbers were small (30 in each cohort).

3.27 The Subcommittee considered the main study investigating the efficacy of adding eltrombopag to immunosuppressive therapy in more detail is the phase III 'RACE' study by the European Group for Blood and Marrow Transplantation in 200 patients, is scheduled to complete its primary endpoint in September 2019, with secondary endpoints by June 2021. This trial seeks to determine whether eltrombopag added to standard immunosuppressive treatment increases the rate of early complete response (Hb >100, ANC >1 and platelet count > 100 $x10^9$/L) to 21% in untreated aplastic anaemia at three months.

3.28 The Subcommittee noted this RACE study is likely to answer the question on whether it is beneficial to initiate eltrombopag earlier. The Subcommittee considered it is likely to become standard of care if this study meets it primary endpoint.

3.29 The Subcommittee considered that in the absence of the RACE result, the Townsley et al. study provides some low-moderate strength with moderate quality evidence for the use of adding eltrombopag to immunosuppression earlier than awaiting confirmation that the patient is refractory to immunosuppressive therapy (the Olnes et al. population).

3.30 The Subcommittee considered that given the high health need of a very small number of patients requiring need maximal supportive care, an amendment to the criteria to allow earlier initiation of eltrombopag is warranted prior to the outcome of the RACE study.

4 Enoxaparin in patients with lower leg immobilisation

Application

4.4 At its meeting in October 2017, the Haematology Subcommittee recommended that widened access to enoxaparin for patients with lower leg immobilisation be discussed as a full agenda item at the next meeting of the Subcommittee. This was prompted by correspondence from a clinician requesting PHARMAC review whether access to enoxaparin should be widened to patient with lower leg immobilisation.

4.5 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

4.6 The Subcommittee **recommended** that the application to widen access to enoxaparin for patients with lower leg immobilisation be declined due to a low health need given the very low absolute risk of symptomatic venous thromboembolism provoked by immobilisation and the lack of evidence for prophylaxis with enoxaparin providing a clinically significant health benefit in the absence of other risk factors.

Discussion

4.7 The Subcommittee noted PHARMAC funds enoxaparin in Section H of the Pharmaceutical Schedule (DHB Hospitals) without restriction, but subject to Special Authority restrictions in the community. The Subcommittee noted there were various initiations for which one months' supply of enoxaparin could be given either in the community or to patients upon discharge from a DHB hospital.

4.8 The Subcommittee noted a Cochrane review of low molecular weight heparin for prevention of venous thromboembolism in patients with lower-limb immobilisation (Zee

AA et al. Cochrane Database Syst Rev. 2017;8:CD006681) which was an update of the review first published in 2008. The Subcommittee noted substantial heterogeneity in the design, measurement and outcomes in the included trials, which were all underpowered. The Subcommittee noted differences in imaging techniques, choice of low-molecular weight heparin rates of unfractionated heparin exposure and a varying approach to including only symptomatic venous thromboembolism. Members noted the possibility of publication bias due to small studies with negative outcomes not being published.

4.9 The Subcommittee noted the recent trial comparing a prophylactic dose of low-molecular-weight heparin as thromboprophylaxis after knee arthroscopy or lower-leg casting versus no anticoagulant therapy (van Adrichem et al. N Engl J Med. 2017;376:515-25). This study concluded that prophylaxis with low-molecular-weight heparin (for the 8 days after knee arthroscopy or during the full period of immobilisation) was not effective for the prevention of symptomatic venous thromboembolism. The Subcommittee noted this was essentially an opposing finding to the Cochrane review. The Subcommittee considered this trial was still underpowered for the low rate of predicted venous thromboembolism, despite being much larger than the other studies in the Cochrane, and that very large patient numbers would have been required to show a statistically significant difference.

4.10 The Subcommittee considered symptomatic venous thromboembolism was more clinically meaningful than non-symptomatic venous thromboembolism. The Subcommittee noted symptomatic venous thromboembolism has a very low incidence (likely to be around 1%) in this setting. The Subcommittee noted symptomatic pulmonary embolism was even rarer with no confirmed deaths in the meta-analysis other than one unconfirmed death in the van Adrichem et al. (2017) paper. The Subcommittee considered the number needed to treat to prevent each symptomatic venous thromboembolism would be very high.

4.11 The Subcommittee concluded that less weight should be placed on the meta-analysis given the issues with heterogeneity of the included studies compared with the pragmatic study design of van Adrichem et al (2017), which the Subcommittee considered well performed study with more clinically relevant end points.

4.12 The Subcommittee considered there was still some uncertainty in the health need of individuals with other risk-factors placing them at higher risk of venous thromboembolism during immobilisation, but noted that rivaroxaban was now funded without restrictions, so may be a more suitable alternative that could be used in this group instead of enoxaparin.