Record of the Haematology Subcommittee of PTAC Meeting held on 29 November 2021

Haematology Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

Note that this document is not necessarily a complete record of the Haematology Subcommittee meeting; only the relevant portions of the meeting record 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.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Subcommittee meeting will be reviewed by PTAC at an upcoming meeting.

PTAC Subcommittees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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1. Attendance

Present

Mark Weatherall (Chair)
Brian Anderson
Paul Harper
Eileen Merriman
Paul Ockelford
Julia Phillips
Lochie Teague

2. The role of PTAC Subcommittees and records of meetings

2.1. This meeting record of the Haematology Subcommittee of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the Pharmac website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

2.2. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Subcommittees and PTAC.

2.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

2.4. The Haematology Subcommittee is a Subcommittee of PTAC. The Haematology Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. The Haematology Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for treatments for Haematology that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for Haematology that differ from the Haematology Subcommittee's, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

Pharmac considers the recommendations provided by both the Haematology Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for Haematology.

3. Record of PTAC meeting held Wednesday, January 30, 2019

3.1. The Subcommittee reviewed the minutes of the PTAC meeting held on 30/1/2019 and agreed that the minutes be accepted.

3.2. The Subcommittee noted the passing this year of Associate Professor John Carter and recognised his valued contributions to the Haematology community and the Haematology Subcommittee over the years.

4. Previous action points/recommendations made

4.1. No action points discussed

5. Emicizumab for patients with severe haemophilia A without factor VIII inhibitors

Application

5.1. The Subcommittee noted the application from Roche Products NZ Ltd for the use of emicizumab (Hemlibra) for the treatment of severe haemophilia A without factor VIII (FVIII) inhibitors.

5.2. The Subcommittee noted that Pharmac sought advice from the Subcommittee about the application following PTAC's review of this application in May 2021, to help inform Pharmac's assessment of emicizumab and the health needs of people with haemophilia A (with or without inhibitors).

5.3. The Subcommittee noted that Pharmac had received feedback regarding the bleed requirements in the funding criteria for emicizumab for severe haemophilia A with inhibitors, and that Pharmac sought advice from the Subcommittee regarding this.

Recommendation

5.4. The Subcommittee noted and acknowledged PTAC's high priority recommendation for emicizumab for severe haemophilia A without FVIII inhibitors, subject to Special Authority criteria, and made no specific recommendation regarding this indication. The Subcommittee considered that a FVIII threshold of 2% could help to target a population with a severe bleeding phenotype who would benefit substantially, and that the renewal approval could be lifelong following successful treatment on initial approval. The Subcommittee therefore considered that the following criteria could target access to emicizumab for patients with severe haemophilia A without inhibitors (changes in **bold** and ~~strikethrough~~ as applicable):

> **EMICIZUMAB**
> **Initial application – (Haemophilia A without inhibitors)** 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 **with a severe bleeding phenotype** (endogenous factor VIII activity, ≤~~1~~**2**%); and
> 2. Emicizumab is to be administered at a dose of 3 mg/kg weekly for 4 weeks followed by the equivalent of 1.5 mg/kg weekly.
>
> **Renewal – (Haemophilia A without inhibitors)** only from a haematologist. Approvals valid ~~for 12 months~~ **without further renewal unless notified** for applications meeting the following criteria:
> 1. The treatment remains appropriate and the patient is benefiting from treatment.

5.5. The Subcommittee considered that access to emicizumab for people with haemophilia A with FVIII inhibitors should be widened by amending the bleeding requirements for this population with inhibitors to require at least one significant bleed within the past six months (rather than the current requirement for six spontaneous bleeds within six months). The Subcommittee considered that the renewal approval could be lifelong following successful treatment on initial approval. The Subcommittee therefore considered that the following criteria could target access to emicizumab for patients with severe haemophilia A with inhibitors (changes in **bold** and ~~strikethrough~~ as applicable):

EMICIZUMAB
Special Authority for Subsidy
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; and
2. **Patient has had at least one significant bleed within the past six months; and** ~~Either:~~
    - ~~2.1. Patient has had 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~~
    - ~~2.2. Patient has had greater than or equal to 2 documented and treated spontaneous bleeds within the last 6 months if on a bypassing agent prophylaxis regimen; and~~
3. 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; and
4. There is no immediate plan for major surgery within the next 12 months; and
5. Either:
    - 5.1. Patient has failed immune tolerance induction (ITI) after an initial period of 12 months; or
    - 5.2. The Haemophilia Treaters Group considers the patient is not a suitable candidate for ITI; and
6. Treatment is to be administered at a maximum dose of 3 mg/kg weekly for 4 weeks followed by the equivalent of 1.5 mg/kg weekly.

Renewal – only from a haematologist. Approvals valid ~~for 6 months~~ **without further renewal unless notified** for applications meeting the following criteria:
Both:

1. Patient has had no more than two spontaneous and clinically significant treated bleeds after the end of the loading dose period (ie 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

Emicizumab for severe haemophilia A with FVIII inhibitors

5.6. The Subcommittee noted that emicizumab has been funded as a prophylactic treatment (subject to the 'Xpharm' rule and funding criteria) for patients with severe haemophilia A who have developed FVIII inhibitors, since 1 December 2020. The Subcommittee noted that, in response to Pharmac's proposal to fund emicizumab for patients with severe haemophilia A who have developed FVIII inhibitors, two haematologists provided feedback regarding the Special Authority criteria. The Subcommittee noted that the respondents considered the proposed criteria was unnecessarily restrictive due to its requirement for patients to demonstrate a number of bleeding events within the previous six months.

5.7. The Subcommittee noted that the bleed requirement in the current Special Authority criteria was derived from the clinical trial evidence, which incorporated a high bleed frequency to include a high-risk population in the trials and to ensure the clinical trial was able to measure and evaluate the effect of emicizumab. The Subcommittee considered that this bleed frequency was an unnecessarily strict measure to use in clinical practice. The Subcommittee considered that patients with high titre inhibitors

(>5BU) will experience frequent bleeds but that not all bleeds would be reported to their care providers. The Subcommittee considered that there is a health need from a single bleed therefore waiting for six bleeds to occur did not reflect good patient care and should not be used for funding criteria. The Subcommittee considered that it would be clinically appropriate for treatment to be initiated after one major bleed and that this would be appropriate for funding criteria.

5.8. The Subcommittee considered that this high bleed frequency requirement would affect a very small number of patients with haemophilia A with inhibitors, as only a small number of people receive emicizumab currently in New Zealand. The Subcommittee considered that widening access to emicizumab for patients with inhibitors who experienced one significant bleed (instead of six) in the previous six months would mean that two or three patients could commence emicizumab at an earlier point in their disease course. The Subcommittee considered there may also be a few patients with inhibitors that have been partially tolerised (ie inhibitors <5 BU) who still experience bleeds, mainly an older adult group with damaged joints, who would not meet the current criteria for emicizumab and considered it was unclear how these patients could be accommodated within the funding criteria.

5.9. The Subcommittee considered that access to emicizumab for people with haemophilia A with inhibitors should be widened by amending the bleeding requirements for this population with inhibitors to require at least one significant bleed within the past six months. The Subcommittee considered that the renewal approval could be lifelong following successful treatment on initial approval, as treatment would not be continued if ineffective or serious adverse events were experienced. The Subcommittee therefore considered that the following criteria could target access to emicizumab for patients with severe haemophilia A with inhibitors (changes in **bold** and ~~strikethrough~~ as applicable):

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Special Authority for Subsidy
Initial application – only from a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

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2. **Patient has had at least one significant bleed within the past six months; and** ~~Either:~~
    - ~~2.1. Patient has had 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~~
    - ~~2.2. Patient has had greater than or equal to 2 documented and treated spontaneous bleeds within the last 6 months if on a bypassing agent prophylaxis regimen; and~~
3. 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; and
4. There is no immediate plan for major surgery within the next 12 months; and
5. Either:
    - 5.1. Patient has failed immune tolerance induction (ITI) after an initial period of 12 months; or
    - 5.2. The Haemophilia Treaters Group considers the patient is not a suitable candidate for ITI; and
6. Treatment is to be administered at a maximum dose of 3 mg/kg weekly for 4 weeks followed by the equivalent of 1.5 mg/kg weekly.

Renewal – only from a haematologist. Approvals valid ~~for 6 months~~ **without further renewal unless notified** for applications meeting the following criteria:
Both:

1. Patient has had no more than two spontaneous and clinically significant treated bleeds after the end of the loading dose period (ie 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.

5.10. The Subcommittee noted that, in May 2021, PTAC reviewed the application for emicizumab prophylaxis for patients with severe haemophilia A without inhibitors and recommended it be funded with a high priority, subject to Special Authority criteria. The Subcommittee noted and acknowledged PTAC's high priority recommendation.

5.11. The Subcommittee noted that PTAC considered that Pharmac should seek advice from the Haematology Subcommittee and the Haemophilia Treater's group regarding, in particular:

- what the treatment paradigm for haemophilia A might be if emicizumab were funded in this setting
- the proposed Special Authority criteria for targeting funding of emicizumab for this population with severe haemophilia A without inhibitors
- any changes to the current Special Authority criteria for emicizumab in the population with inhibitors
- the assumptions around direct and indirect health system costs and savings (including any changes in administration requirements venous line placement)
- the likely uptake of emicizumab prophylaxis in this population without inhibitors
- the likely change in FVIII usage in the absence of emicizumab funding in this population without inhibitors

5.12. The Subcommittee noted that the health needs of people with haemophilia A has been described by PTAC in May 2021 and by the Haematology Subcommittee in January 2019. The Subcommittee considered that the estimated number of patients with severe Haemophilia A without inhibitors in New Zealand (around 135 to 150 people, roughly one-third of whom are children) was reasonable. The Subcommittee considered that it was reasonable to assume 100% of paediatric patients and 80% of adult patients with severe haemophilia A without inhibitors were currently on FVIII prophylaxis. The Subcommittee considered that the target patient population numbers were hard to estimate as not all bleeds are reported, assessment is subjective, and there is some variation in both clinician behaviour and FVIII test results.

5.13. The Subcommittee considered that FVIII of <1% was a reasonable threshold for identifying severe haemophilia A in patients with frequent bleeds, however, there would be a small number of patients with FVIII between 1% and 2% with moderate haemophilia and a severe bleed phenotype who have a similar need due to the limitations and inconveniences of current prophylactic treatments. The Subcommittee considered that using a threshold of 2% instead of 1% would increase the target population by only a small number of patients. The Subcommittee noted that there will be patients with >2% FVIII who experience a lot of bleeds, however, considered that only a small proportion of patients with FVIII between 2% and 5% require prophylaxis. The Subcommittee noted that increasing the level of FVIII required to access funded emicizumab above 1% could make assessment subjective and dependant on clinician behaviour. On balance, the Subcommittee considered that a threshold of ≤2% for funding criteria would help to target those who would reasonably be expected to benefit most from emicizumab prophylaxis.

5.14. The Subcommittee noted that treatment onset is in childhood and that most patients with severe haemophilia A without inhibitors receive prophylaxis with FVIII replacement administered intravenously (IV) either with short half-life recombinant about three times per week, or extended half-life recombinant administered about two times per week. The Subcommittee considered that current prophylactic treatment is effective in significantly reducing the incidence of bleeds; however, the Subcommittee considered that this frequent IV administration, which totals roughly 100 to 180 infusions per year, has a significant impact on patients and their family/whānau. The Subcommittee noted that regular infusions for FVIII prophylaxis are not given in hospital and the proportion of bleeds treated in hospital is small, with most bleeds instead treated at home.

5.15. The Subcommittee considered that FVIII prophylaxis is administered via a central venous access device such as a port-a-cath, or port, for many children until about eight to ten years of age when prophylaxis switches to peripheral vein access, and considered that such central access would be revised at least once before that time. The Subcommittee considered that ports require significant resource for insertion, removal and infusions. The Subcommittee considered that current prophylaxis with FVIII replacement conveys a risk of morbidity to the patient due to catheter-related infection, which occurs in about 25% of patients. The Subcommittee noted that a catheter-related infection may require intensive inpatient treatment with antibiotics, and catheter removal and replacement under anaesthesia. The Subcommittee considered that issues with administration of current IV prophylaxis also include poor venous access due to administration of prophylactic and episodic treatments over time and needle phobia, especially in older patients. The Subcommittee considered that patients may require short anaesthesia in cases of challenging venous access. The Subcommittee considered that there is a significant impact on family/whānau when it is unclear whether prophylaxis is being effectively administered, resulting in uncertainty around coverage for potential bleeding events.

5.16. The Subcommittee considered that FVIII usage in New Zealand comes at a very high cost and is approaching peak usage, with the amount of FVIII usage unlikely to increase significantly in the future. The Subcommittee considered that a trough target level of about 1% is generally used for prophylaxis in New Zealand although the target level for prophylaxis was unclear, with some treatment guidelines overseas recommending a trough target level of up to 5%, which would come at a significant cost. The Subcommittee noted that there is no universal prophylaxis regimen and considered that usage is roughly 100 units per kg per week for most patients. The Subcommittee considered that effective FVIII prophylaxis for patients with severe haemophilia A without inhibitors can decrease hospitalisations, prevent life-threatening events such as intracranial bleeds, and significantly reduce bleeds to about two per year. However, the Subcommittee considered that effective FVIII prophylaxis will not eliminate all bleeds and that patients with pre-existing joint disease may develop arthritis and require surgery in early adulthood. Overall, the Subcommittee considered that current FVIII prophylaxis is effective at reducing bleeds but has significant limitations and is inconvenient to patients with severe haemophilia A and their family/whānau.

5.17. The Subcommittee noted that inhibitors to FVIII develop in about 30% of New Zealand patients and that high-titre inhibitors are present in about 15%; while these occur in a small proportion of patients, the Subcommittee considered that this conveys significant issues for those individuals including reduced survival. The Subcommittee considered that management of patients with inhibitors is significantly different to the treatment of those without inhibitors, requiring the use of bypassing agents and immune tolerance induction (ITI) to remove the inhibitors in many cases.

The Subcommittee considered that patients with inhibitors who experience one or two bleeds per month receive about a 70% reduction in the number of bleeds with FVIII inhibitor bypassing fraction [activity] (FEIBA) prophylaxis, and about an 85% reduction with emicizumab. The Subcommittee considered that there is an unmet need in this population even with the use of bypassing agents or ITI.

5.18. The Subcommittee noted that emicizumab is a monoclonal antibody that mimics FVIII but does not cause FVIII inhibitors to develop nor is it inhibited by FVIII. The Subcommittee noted that emicizumab is highly bioavailable and has a long half-life of about one month, compared to that of short- or extended half-life FVIII products which is less than 24 hours. The Subcommittee noted evidence from pharmacokinetics studies (Donners et al. Clin Pharmacokinet. 2021; doi: 10.1007/s40262-021-01042-w. Online ahead of print; Schmitt et al. Thromb Haemost. 2021;121:351-60) and considered that after the initial loading dose, emicizumab's steady state fortnightly or four-weekly dosing results in an improvement in haemostasis that is roughly equivalent to FVIII activity levels of about 15% (20-30% based on clinical experience). The Subcommittee considered that this was equivalent to a mild haemophilia phenotype, providing greater coverage for breakthrough bleeds than trough levels on FVIII prophylaxis (FVIII activity of less than 5%). The Subcommittee noted that emicizumab is administered subcutaneously, rather than intravenously in the case of FVIII prophylaxis, and that the dosing intervals appear not to affect its efficacy.

5.19. The Subcommittee noted that the key evidence for emicizumab comes from the HAVEN 1-4 studies which were described by PTAC in May 2021 and the Haematology Subcommittee in January 2019. The Subcommittee noted that a two-year combined analysis of long-term outcomes with emicizumab prophylaxis for haemophilia A with/without FVIII inhibitors in 401 patients from the HAVEN 1–4 studies was reported by Callaghan et al. (Blood. 2021;137:2231-42). The Subcommittee noted that 192 participants (47.9%) had FVIII inhibitors at the studies' baseline timepoints and that a high proportion (about 60%) of participants across the four HAVEN trials had pre-existing joint disease. The Subcommittee noted that about 70% of patients had zero treated bleeds across the four studies over about two years, with the reduction increasing over time.

5.20. The Subcommittee noted that the HAVEN 3 trial provided the key evidence for the population without inhibitors and considered that a key benefit of emicizumab was the significant reduction in bleeding events compared with currently available FVIII prophylaxis (68% reduction in treated bleeds with emicizumab prophylaxis compared with the pre-emicizumab treatment period when 34 patients received FVIII prophylaxis; annualised bleed rate 1.5 vs 4.8; rate ratio 0.32; 95% CI: 0.20 to 0.51) (Mahlangu et al. N Engl J Med. 2018;379:811-22). The Subcommittee noted that about 60% of HAVEN 3 participants were receiving on-demand treatment rather than prophylaxis and considered this likely accounted for the high bleed rate in this cohort. The Subcommittee noted that target joints resolved in >90% of patients and considered this was good efficacy for a population with chronic synovitis which is associated with frequent bleeding. The Subcommittee considered that essentially eliminating spontaneous bleeds in most patients would be life changing, although noted that older adults would still require surgery due to pre-existing joint damage.

5.21. The Subcommittee considered that young patients receiving emicizumab prophylaxis would have a mild disease phenotype, therefore would not experience severe haemophilia symptoms which otherwise might limit high-risk activities that could lead to traumatic bleeds. The Subcommittee noted that only 5% of HAVEN 3 participants were less than 18 years of age, however, considered that real-world

experience was contributing to the evidence for emicizumab use in younger patients and that the benefits were supported by further publications (Pipe et al. Lancet Haematol. 2019;6:e295-e305; Shima et al. Haemophilia. 2019;25:979-87; Young et al Blood 2019;134: 2127).

5.22. The Subcommittee considered that emicizumab prophylaxis in patients with haemophilia A without inhibitors would avoid the development of inhibitors in a majority of patients and that this was a significant benefit, subsequently avoiding the need for patients to undergo ITI. The Subcommittee considered that this benefit would be more pronounced for younger children if they commenced treatment with emicizumab instead of trialling FVIII prophylaxis, with the potential to develop inhibitors and subsequently require ITI. The Subcommittee considered that it was unclear at treatment commencement which patients would develop inhibitors due to repeat exposure to FVIII and considered that emicizumab prophylaxis would avoid development of inhibitors for most patients. The Subcommittee considered that it would be very rare but acknowledged the potential for patients to develop FVIII inhibitors in future due to their previous exposure to FVIII or re-exposure to FVIII for management of a bleeding event.

5.23. The Subcommittee considered that avoiding the need for port insertions and associated risks and complications was a major benefit of emicizumab over currently funded FVIII prophylaxis, especially in young children. The Subcommittee considered that another benefit was the low incidence of important adverse events (AEs) with emicizumab, as reported in the clinical trial evidence and from clinical practice in the population with inhibitors. The Subcommittee considered that no additional AEs would be expected in paediatric patients based on the available evidence and real-world experience. However, the Subcommittee noted the risk of thrombotic microangiopathy with FEIBA in emicizumab-treated patients and considered that patients using emicizumab would not receive FEIBA. The Subcommittee considered that there was no identifiable subgroup of patients with haemophilia A who could be prospectively considered to be clinically unsuitable for treatment with emicizumab.

5.24. The Subcommittee was made aware of evidence that emicizumab anti-drug antibodies (ADAs) were reported in 4/18 (22%) of phase I/II trial patients on emicizumab, all of which were non-neutralising (Shima et al. Blood Adv. 2017;1:1891-9), and evidence that ADAs were reported in 14/398 (3.5%) phase III patients in the HAVEN studies, of which 3 were neutralising and emicizumab was discontinued in one patient (0.25%) where emicizumab disappeared from their circulation and recurrent bleeding occurred [Paz-Priel et al. Blood. 2018;132(suppl_1)]. The Subcommittee considered it was unclear whether four-weekly dosing was associated with a higher incidence of ADA production.

5.25. The Subcommittee considered that the clinical trial evidence was not compelling for an overall benefit in quality of life (QOL) but noted that 94% of HAVEN 3 participants who responded to the EmiPref survey (71% of those eligible to complete the survey) reported a preference for emicizumab (Mahlangu et al. N Engl J Med. 2018;379:811-22). However, the Subcommittee considered that there would likely be significant QOL benefits at an individual level and that additional benefits of emicizumab over FVIII prophylaxis would include patient acceptability and well-being, stress reduction and improved ability to cope with treatment. The Subcommittee considered that the use of emicizumab in the currently funded population with FVIII inhibitors was associated with an increase in patient ability to do more usual activities without developing joint damage and considered that similar results would be expected for

patients without inhibitors given emicizumab appears to result in a mild disease phenotype.

5.26. The Subcommittee also noted the following evidence regarding emicizumab:

- Reyes et al. Curr Med Res Opin. 2019;35:2079-87
- Ebbert et al. Haemophilia. 2020;26:41-6
- Shima et al. Haemophilia. 2021;27:81-9

5.27. Overall, the Subcommittee considered that the evidence for emicizumab in patients with haemophilia A without inhibitors from well-designed and implemented studies and from clinical experience in the population with inhibitors indicated that emicizumab prophylaxis provides meaningful benefits to patients and family/whānau. The Subcommittee considered that these benefits would be expected to translate into QOL benefits especially for young children and/or those with poor venous access. The Subcommittee noted that the HAVEN studies have further long-term follow-up data to come, however, considered that reasonable follow-up evidence was available to inform assessment of efficacy at this time.

5.28. The Subcommittee considered that the patients with severe haemophilia A without inhibitors who could benefit most from a transition to emicizumab would be children (thus avoiding ports and associated infections), patients with poor venous access, and those with FVIII of ≤2% and a severe bleed phenotype (who are increasingly affected by arthritis and bleed a lot as they age). The Subcommittee considered that subcutaneous administration had substantial benefits over IV treatment for several reasons, as noted by PTAC in May 2021, and considered that avoiding port infections in particular would be clinically meaningful. The Subcommittee considered that subcutaneous treatment may significantly help compliance and avoid issues associated with venous access and IV administration.

5.29. The Subcommittee considered that implementation of emicizumab (ie upscaling of the current direct distribution arrangement) for this population would not be associated with any particular difficulties. The Subcommittee considered that an effective transition plan would be needed to manage the change from FVIII prophylaxis to emicizumab, with support from the Haemophilia Treater's Group.

5.30. The Subcommittee noted that FVIII testing is required to manage patient care peri-operatively and to check for inhibitors. The Subcommittee noted that the FVIII chromogenic assays currently available use human reagent at four of the six treating centres around the country, whereas a bovine reagent assay is used at two centres and can be used for all chromogenic FVIII assay indications. Members considered that if a bovine reagent chromogenic FVIII assay were required at most centres to determine FVIII levels to access funded emicizumab and to facilitate safe surgery for patients receiving emicizumab, this would come at a significant cost to the health system (ie tens of thousands of dollars per centre changing from human to bovine reagent).

5.31. The Subcommittee noted that the ELISA immunoassay kit is not available in New Zealand and considered that this would be necessary to measure drug concentrations and administer treatment, especially if there were consideration of reducing dose alongside assessment of clinical outcomes for individuals. Members considered that this test would be most relevant for a rare patient receiving a suboptimal response in whom anti-emicizumab antibodies would be suspected and

considered that introducing this assay at one centre would be sufficient to provide testing for the country. The Subcommittee considered that provision of these kits by the supplier alongside emicizumab funding would significantly benefit patient management.

5.32. The Subcommittee considered there would be direct benefits to the health system from the differences between IV and subcutaneous treatment administration, specifically due to the small number of patients not requiring a port for treatment (although very important for individual patients) and the substantial change in requirements for treatment, especially with the four-weekly subcutaneous administration compared to IV infusions a couple of times each week. The Subcommittee considered that emicizumab would likely replace long-acting FVIII prophylaxis in all patients with severe haemophilia A (depending on the FVIII threshold used) and there would be a significant reduction in the annual bleed rate with a high proportion having zero bleeds each year, resulting in significantly less short-acting FVIII usage on demand. The Subcommittee considered that this could benefit the health system and blood service if there was a substantially reduced requirement for FVIII products, which is approaching peak usage following the shift from short half-life products to extended half-life products and is unlikely to significantly increase in future. However, members considered that gradual growth in FVIII usage could occur due to population ageing and growth in the absence of an alternative therapy.

5.33. The Subcommittee considered that emicizumab-treated patients would have less engagement with the health system due better disease control.. The Subcommittee considered that this change would benefit the overall health system as this patient population currently requires close management and substantial engagement due to their difficult disease, especially in children. The Subcommittee considered that savings would result from avoiding the development of FVIII inhibitors in the vast majority, given the substantial treatment and management requirements for people with inhibitors and that this would be a key benefit of funding emicizumab in this population. The Subcommittee considered that there would be no significant savings for treatment administration given that regular infusions for FVIII prophylaxis are not given in hospital and the proportion of bleeds treated in hospital is small.

5.34. The Subcommittee considered that no long-acting FVIII would be required for patients with severe haemophilia A receiving emicizumab and that short-acting FVIII would only be required for management of surgery and significant bleeds (eg into joints with pre-existing damage and only occurring with a greater degree of trauma than for FVIII prophylaxis). The Subcommittee considered that one or two doses of short acting FVIII would be required for these major traumatic bleeds and any major surgery requirements, with usage similar to that of patients with mild haemophilia A (approximately 1.4 events per patient per year, totalling 200 short half-life FVIII infusions per year for 135 patients with severe haemophilia A). The Subcommittee noted that this is an ageing population with potential attendant requirements for surgery and considered that there may be occasional additional usage of FVIII for patients wanting to be more active (eg peaks of FVIII to play sport). The Subcommittee considered it was unlikely that surgery requirements would significantly change with the funding of emicizumab in the short- to medium-term.

5.35. The Subcommittee considered that, as ELISA immunoassay kits are not available to monitor and inform lesser dosing, clinicians would not routinely use doses of less than 1.5mg/kg per week except perhaps in a very small child due to syringe size until resolved with sufficient growth. The Subcommittee considered that some centres may round down doses if needed due to syringe size or delay increasing a

syringe size with patient growth if a patient was managing well. However, the Subcommittee considered that dosing would likely increase over time as children grow using the clinical trial dosing, with the dosing schedule extended over time to higher doses at two-weekly or four-weekly intervals. The Subcommittee considered that high doses of emicizumab would not be used to manage breakthrough bleeds. The Subcommittee considered there was insufficient evidence to support a lower dosing regimen than that used in the pivotal trials.

5.36. The Subcommittee considered that adherence to emicizumab would be high, especially for four-weekly administration, and that the estimate of 90% was reasonable given this population with lived experience of severe disease will likely be very compliant. The Subcommittee considered that uptake of emicizumab prophylaxis in the population without inhibitors in New Zealand would quickly approach 100% within the first year due to clinician preference for its use, although considered it was possible an outlier patient may prefer to continue on FVIII prophylaxis (likely short-term). However, members noted that about 80% of patients on FVIII prophylaxis in Australia transitioned to emicizumab when available, although the reasons for this reduced uptake were unclear. The Subcommittee considered that uptake in New Zealand would likely be higher than in other countries due to the small and close-knit haemophilia community, and the involvement of the Haemophilia Treaters Group and those managing the care of these patients.

5.37. The Subcommittee considered that developing inhibitors on emicizumab would be unlikely but if this were to occur, patients would most likely be of older age. The Subcommittee considered that patients who developed inhibitors would avoid all FVIII and FEIBA, and would continue on emicizumab. The Subcommittee considered that the inhibitor titre would likely subside and the patient may require the bypassing agent eptacog alfa (recombinant factor VIIa). The Subcommittee considered that ITI might not be relevant although if this were undertaken it would be expensive in an older patient due to weight-based dosing. The Subcommittee noted that gene therapies in future may change the treatment paradigm for this population.

5.38. The Subcommittee noted the proposed Special Authority criteria and considered that a FVIII threshold of 2% could help to target a population with a severe bleeding phenotype who would benefit substantially, and that the renewal approval could be lifelong following successful treatment on initial approval. The Subcommittee therefore considered that the following criteria could target access to emicizumab for patients with severe haemophilia A without inhibitors (changes in **bold** and ~~strikethrough~~ as applicable):

> **EMICIZUMAB**
> **Initial application – (Haemophilia A without inhibitors)** only from a haematologist.
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> All of the following:
> 1. Patient has severe congenital haemophilia A **with a severe bleeding phenotype** (endogenous factor VIII activity, ≤~~1~~**2**%); and
> 2. Emicizumab is to be administered at a maximum dose of 3 mg/kg weekly for 4 weeks followed by the equivalent of 1.5 mg/kg weekly.
>
> **Renewal – (Haemophilia A without inhibitors)** only from a haematologist. Approvals valid ~~for 12 months~~ **without further renewal unless notified** for applications meeting the following criteria:
> 1. The treatment remains appropriate and the patient is benefiting from treatment.

5.39. The Subcommittee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for emicizumab if it were to be funded in New Zealand for severe haemophilia A without inhibitors. This PICO captures key clinical aspects of the proposal and may

be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Subcommittee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Patients with severe congenital haemophilia A with a severe bleeding phenotype (endogenous factor VIII activity ≤2%)
Intervention	Emicizumab 3mg/kg weekly for 4 weeks, followed by 1.5mg/kg per week (or equivalent) Adherence assumed to be 90% based on Mahajerin et al. Blood 2020;136 (Supplement 1):13 real-world study, and long-term data from HAVEN 1-4 Callaghan et al. Blood 2021;137:2231-42
Comparator(s)	Episodic / prophylactic use of FVIII Supplier assumes 100% of paediatric patients currently receive prophylactic treatment, and that 80% of adult patients receive prophylactic treatment (the rest receive episodic treatment with FVIII) Supplier assumes roughly one-third of patients are children (<18 years), two-thirds are adults
Outcome(s)	Versus episodic treatment: reduction in number of bleeds requiring treatment; improved quality of life; extrapolated to assume reduction in mortality based on relationship between haemophilia severity and mortality in Darby et al. Blood 2007;110:815–825 Versus prophylactic treatment: reduction in number of bleeds requiring treatment; no mortality or quality of life gains Potential small quality of life gain from psychological benefit associated with fewer bleeds and more suitable treatment Additional health system savings from: - reduction in patients developing inhibitors and associated cost of bypassing agents - reduction in requirements for insertion of central lines - reduction in need for specialist haematologist care
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	