MSAC Application 1805

Concizumab for routine prophylaxis to prevent bleeding in patients with Haemophilia B

Applicant: NOVO NORDISK PHARMACEUTICALS PTY LTD

PICO Confirmation

Summary of PICO criteria to define question to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for prophylactic treatment with concizumab in patients with congenital Haemophilia B who have developed Factor IX inhibitors

Component	Description
Population	Patients ≥ 12 years of age with congenital Haemophilia B (cHMB) who have developed Factor IX (FIX) inhibitors and where prophylaxis is required to prevent or reduce the frequency of bleeding.
Intervention	Prophylaxis with concizumab (Alhemo®) plus on demand bypassing agents (BPAs) to treat bleeds.
Comparator/s	On demand treatment with the BPA recombinant activated human Factor VIIa (rFVIIa). Short-term prophylaxis (up to 3 months) with the BPA rFVIIa.

Outcomes	Safety
	• Incidence and severity of adverse events
	  ○ Thrombosis
	• Mortality
	• Emergence of anti-concizumab antibodies
	Effectiveness
	• Primary effectiveness
	  ○ Reduction in number of bleeds over time (bleed rate)
	  ○ Prevention of bleeds
	• Secondary effectiveness
	  ○ Responder status
	  ○ Other bleeding related outcomes such as: number of joint bleeds over time; number of target joint bleeds over time; individual bleed rate compared to historical bleed rate; and number of treated bleeds per month or year.
	  ○ Perioperative use of therapy and outcomes
	  ○ Health-related quality of life
	  ○ Joint health outcomes
	  ○ Chronic pain associated with haemophilia
	  ○ Number of missed days of work/activity/school
	Healthcare resources
	• Costs of delivering the intervention
	• Costs of managing adverse events or breakthrough bleeding
	• Cost offsets
	• Cost per quality-adjusted life year (QALY) gained
	Total Australian government healthcare costs
	• Total cost to the National Blood Authority (NBA)
	• Total cost to other government health budgets

Component	Description
Assessment questions	What is the safety, effectiveness and cost-effectiveness of prophylaxis with concizumab plus on demand BPAs versus on demand BPAs +/- short-term prophylaxis with rFVIIa in patients aged ≥12 years with cHMB and FIX inhibitors?

Purpose of application

An application requesting public funding through listing on the National Blood Authority's (NBA's) National Product Price List (NPPL) of concizumab (Alhemo®) for routine prophylaxis to prevent bleeding in patients with congenital Haemophilia B (cHMB) with inhibitors was received from Novo Nordisk Pharmaceuticals Pty Ltd by the Department of Health.

Public funding for blood and blood-related products is facilitated via the National Blood Agreement and managed by the NBA on behalf of all governments. Schedule 4 of the Agreement provides for evidence-based evaluation and advice to governments to support decisions regarding changes to products funded under the National Blood Agreement, including assessment by the Medical Services Advisory Committee (MSAC) where required.

The use of concizumab is proposed to result in superior health outcomes (prevention and reduction of bleeds, improved quality of life) compared to the comparator.

The use of concizumab is proposed to result in at least non-inferior safety compared to the comparator.

PICO criteria

Population

The proposed population is adolescent and adult patients (≥12 years) with cHMB who are positive for Factor IX (FIX) inhibitors and where prophylaxis is required to prevent or reduce the frequency of bleeding.

PASC noted and accepted the applicant's comments on the pre-PASC PICO that the population requiring short-term peri-operative prophylaxis should be removed from the proposed population.

Disease characteristics

Congenital haemophilia is a rare bleeding disorder caused by deficiencies in coagulation factors due to mutations in clotting factor genes. The incidence in Australia is reported as 11.60 per 100,000 (ABDR, 2023). Prevalence varies globally; however, it has increased over time and is higher in high income countries (Stonebreaker et al. 2010). There are 2 main types of congenital haemophilia, with type A (cHMA) accounting for 80–85% of the total prevalent population and type B (cHMB) around 15% (Srivastava et al. 2020). The most recent Australian registry data reports 2,681 patients with cHMA and 621 patients with cHMB (ABDR, 2023).

Congenital HMB is characterised by partial or complete deficiency in the activity of the essential coagulation factor, FIX, due to X-linked heritable variants of the FIX gene. It occurs primarily in males, with females typically being carriers with a mild or absent phenotype. Acquired HMB, due to the formation of anti-FIX antibodies occurring in an individual without cHMB, is out of scope for this application.

For patients with cHMB, bleeding tendency generally correlates with FIX concentrations, therefore, severity and risk of bleeding is classified according to endogenous plasma FIX concentrations. FIX concentrations <1% are classified as severe disease, 1–5% as moderate disease and >5–40% as mild disease (Srivastava et al. 2020). However, individuals may exhibit severe bleeding irrespective of FIX concentrations.

Repeated bleeding episodes, especially joint bleeds (haemarthrosis), are a major cause of significant morbidity and decreased quality of life in people living with cHMB. Although infrequent, intracranial and gastrointestinal bleeding, and bleeding into the neck and throat, can be life-threatening (AHCDO & NBA, 2016).

Treatment for cHMB consists of intravenous (IV) FIX replacement therapy, using either plasma-derived or recombinant FIX, administered prophylactically or on demand (i.e. when bleeds occur or prior to surgery) (Table 2). When used for prophylaxis, standard half-life FIX products require intravenous (IV) administration 2-3 times per week whereas extended half-life FIX may enable patients to infuse every 7 to 14 days (Srivastava et al. 2020).

Table 2 FIX replacement products available on the National Product Price List

Product	Supplier Dosage	Cost
MonoFIX Factor IX (Plasma derived – domestic) Standard half-life	CSL Behring 1000 IU	$1,064.04
BeneFIX Factor IX (recombinant – imported) Standard half-life	Pfizer Australia 250 IU/ 500 IU/ 1000 IU/ 2000 IU/ 3000 IU	Not disclosed
ALPROLIX Factor IX (recombinant – imported) Extended half-life	Sanofi-Aventis 250 IU/ 500 IU/ 1000 IU/ 2000 IU/ 3000 IU/ 4000 IU	Not disclosed

FIX = Factor IX; IU = international units
Source: National Product Price List

Haemophilia B with inhibitors

Inhibitors are immunoglobulin G (IgG) antibodies that develop in response to exogenous FIX and neutralise FIX clotting function. They occur in up to 5% of patients with cHMB and are almost exclusively seen in patients with severe cHMB and very rarely in the milder forms (Srivastava et al. 2020). The development of inhibitors is one of the most serious and challenging complications of cHMB and the loss of treatment effect leads to reduced quality of life and higher treatment costs (D'Angiolella et al. 2018).

Inhibitor development in cHMB is also associated with anaphylaxis or severe allergic reactions to exogenous FIX in 50% of subjects and this can be the first symptom of inhibitor development. Patients with cHMB and inhibitors receiving high-dose FIX for immune tolerance induction may also develop nephrotic syndrome (Srivastava et al. 2020).

For children, screening for inhibitors should take place once every 5 exposure days until 20 exposure days, then every 10 exposure days between 21 and 50 exposure days, and at least two times a year until 150 exposure days. For adults with more than 150 exposure days, apart from a 6–12 monthly review, any failure to respond to adequate FIX concentrate replacement therapy in a previously responsive patient is

an indication to assess for an inhibitor. Inhibitors should also be assessed in all patients who have been intensively treated for more than 5 days, within 4 weeks of the last infusion (AHCDO & NBA, 2016).

Inhibitors are measured by the Nijmegen-modified Bethesda assay. The definition of a positive inhibitor is a Bethesda titre of greater than 0.3 Bethesda units (BU) for FIX. Inhibitor titre can be categorised as either high responding (≥5.0 BU/ml), which tends to be persistent, or low responding (<5.0 BU/ml), which tends to be transient. A transient inhibitor is defined as a positive inhibitor that drops below the definition threshold within 6 months of initial documentation without any change in treatment regimen, and despite antigenic challenge with FIX. High responding inhibitors may become undetectable after a prolonged period without FIX treatment but reoccur after a rechallenge (an anamnestic response) (Srivastava et al. 2020).

Treatment and management

Optimal management is individualised based on inhibitor titre, clinical response, infusion reactions and bleed frequency. In Australia, most people living with cHMB receive care via a dedicated haemophilia treatment centre (HTC), typically located within a hospital, and comprising a team of specialist health professionals (haematologists, nurses, psychosocial workers, physiotherapists, laboratory services etc.) with expertise in managing and treating cHMB (NBA, 2025).

Inhibitor eradication through immune tolerance induction (ITI) can be attempted using administration of high doses of FIX; however, it has a low success rate in cHMB (30 to 35%) and is complicated by the risk of anaphylaxis and nephrotic syndrome. In its current guideline document, the World Federation of Haemophilia (WFH[1]) states that it is unable to make a recommendation on the use of ITI in cHMB as experience is limited (Srivastava et al. 2020). The Australian Bleeding Disorders Registry (ABDR) reported use of FIX for tolerisation in cHMB from 2018-19 to 2021-22 but not in 2022-23 (Table 4). The application states that it is not a mainstay of treatment in Australia.

For patients with cHMB and low-responding inhibitors, acute bleeds can be managed with continuing use of FIX product, at a higher dose, provided there is no allergic response (Srivastava et al. 2020).

For acute bleeds in patients with cHMB and high-responding inhibitors and/or allergic reactions, a bypassing agent (BPA) is used. The two BPAs available in Australia are listed in Table 3. In cHMB, recombinant activated Factor VIIa (rFVIIa) is preferred over activated prothrombin complex concentrate (aPCC) due to the presence of FIX in the latter, which may trigger anaphylaxis (this is reflected in the infrequent use of aPCC in patients with cHMB recorded in the ABDR; Table 4).

When used to control bleeding, rFVIIa is administered every 2-3 hours and then every 3-12 hours if necessary. Recombinant FVIIa is also indicated for surgical prophylaxis and for short-term prophylaxis for up to 3 months in patients with a high bleeding frequency (≥4 bleeding episodes per month). Short-term prophylactic treatment is once daily via IV infusion.

The ABDR notes, with respect to BPAs (in cHMA and cHMB), that "predicting or interpreting changing demand trends is not possible with any accuracy, as the product is only used in a small number of patients each year. Use patterns will vary from year to year and will not only depend on the number of patients treated, but their severity of disease, the potency of inhibitors, whether secondary prophylaxis is

[1] The WFH Guidelines have been adopted in Australia by the Australian Haemophilia Centre Directors' Organisation (AHCDO) with some amendments/additions for the Australian context.

practiced, the number and severity of spontaneous bleeds, and the amount of elective surgery undertaken in this patient group" (ABDR, 2022).

The applicant advised (pre-PASC meeting, 27 June 2025) that not all rFVIIa use is recorded in the ABDR, and that uptake varies due to the small number of patients, some of whom are enrolled in trials for investigational products. Therefore, no trend should be inferred from Table 4.

Table 3 Bypassing agents on the National Product Price List

Product	Supplier Dosage	Cost
NovoSeven (eptacog alfa) Factor VIIa (recombinant - imported)	Novo Nordisk Pharmaceuticals Pty Ltd 1mg/2mg/5mg and 8mg	$1,250.00 per mg
FEIBA Factor VIII Activated Prothrombin Complex Concentrate APCC) (plasma derived - imported)	Takeda Pharmaceuticals Australia 500 IU/ 2500IU	$1,140.00 per 500 IU

IU = international units; mg = milligram
Source: National Product Price List

Table 4 Volume of BPA product and FIX for tolerisation used by adult patients with cHMB from 2018-19 to 2022-23

Product	2018-19	2019-20	2020-21	2021-22	2022-23
Factor VIIa (NovoSeven) (mg)	1,902	5,444	2,396	1,000	120
aPCC (FEIBA) (IU)	-	130,000	-	-	-
FIX (for tolerisation) (IU)	488,000	465,000	259,000	26,500	-

aPCC = activated prothrombin complex concentrate; BPA = bypassing agent; cHMB = congenital Haemophilia B; FIX = Factor IX; IU = international units; mg = milligram
Source: ABDR Annual Reports

Emicizumab (Hemlibra), a monoclonal antibody that mimics the function of FVIII, was listed on the NPPL in November 2020. Its introduction has led to a marked reduction in the use of FVIII, rFVIIa and aPCC, with all declining (ABDR, 2022). However, due to the mechanism of action being specific to cHMA, emicizumab is not suitable for use in cHMB. Therefore, therapeutic options available for patients with cHMB and inhibitors remain more limited compared to those available for patients with cHMA and inhibitors.

PASC raised two key issues regarding the proposed population.

First, PASC noted that while the Therapeutic Goods Administration (TGA) has approved concizumab for all patients with cHMB with and without FIX inhibitors, the current application is limited to patients with cHMB and FIX inhibitors only. This represents a very small population - fewer than 15 patients - some of whom are already accessing therapy through compassionate use or clinical trials.

The applicant explained that they have focused on the population with the highest clinical need and emphasised the importance of not delaying access to therapy for these patients. The applicant's clinical expert also highlighted that currently no subcutaneous treatments are available for patients with cHMB without FIX inhibitors, in contrast to HMA, where emicizumab is available and extensively utilised. Given

the challenges of venous access for some patients, there is a clear clinical need for a subcutaneous prophylactic option for patients with cHMB without FIX inhibitors.

Given that concizumab is approved for a broader population with a demonstrated clinical need, PASC expressed concern that restricting the application to a narrow subgroup is inefficient. PASC recalled that the initial application for emicizumab (MSAC Application 1510) that proposed treatment for patients with HMA and FVIII inhibitors was not supported by MSAC until evidence was provided for both patient groups (HMA with and without FVIII inhibitors) (MSAC Application 1510.1). PASC cautioned that the Evaluation Subcommittee (ESC) and MSAC may consider the fragmented approach as contributing to uncertainty, whereas a combined approach would be more compelling.

Furthermore, PASC noted that the NBA has historically not supported differential pricing across patient subgroups.

PASC strongly recommended a combined population approach, advising that an application that includes all patients with cHMB would not require a second PASC assessment or delay the overall process. The department and the committees indicated their willingness to provide support to achieve this outcome. PASC noted that expanding the proposed population to all people with severe cHMB would increase the eligible population from under 15 to 114 patients approximately.

The second issue raised by PASC concerned the potential impact of gene therapy on the proposed population – specifically, whether it would alter the population developing FIX inhibitors. PASC noted that MSAC had recently evaluated an application for public funding of the gene therapy etranacogene dezaparvovec (Hemgenix®) for adult patients with moderately severe or severe cHMB without FIX inhibitors (MSAC Application 1728.1) and that if this were funded, this may impact the population with inhibitors . The applicant's clinical expert noted that, to date, no patients who have received etranacogene dezaparvovec have developed FIX inhibitors. Furthermore, the development of FIX inhibitors tends to occur during the paediatric period (first 150 days of exposure). Therefore, the population with cHMB with FIX inhibitors is likely to remain stable.

Estimate of patient numbers

According to the ABDR 2019-20 report, there are <5 patients with cHMB and inhibitors in Australia (ABDR, 2020). The application states there is a total estimated patient population of 4 based on feedback from HTCs; 3 adult patients and one adolescent patient (≥12 years of age).

At the PASC meeting, the applicant's clinical expert stated that the population of patients with cHMB and FIX inhibitors was less than 15 in Australia, differing from the <5 patients estimate provided in the application. PASC requested this discrepancy be clarified in the assessment.

Intervention

Concizumab is a monoclonal antibody against tissue factor pathway inhibitor (TFPI). TFPI is a regulator of the coagulation system that inhibits tissue-factor induced coagulation, particularly Factor Xa (FXa) and Factor VIIa (FVIIa). Concizumab binds to TFPI and enhances coagulation through directly preventing FXa inhibition and indirectly preventing FVIIa inhibition. This permits greater thrombin formation to promote clot formation independently of FIX (and FVIII); its action is therefore not influenced by the presence of inhibitors to these factors.

Dosage and frequency of treatment

Concizumab is administered as a daily subcutaneous injection using a multidose disposable prefilled pen, which consists of a 1.5 mL or 3 mL glass cartridge sealed in a pen-injector (similar to commonly used insulin pen injectors) (Figure 1). A doctor or nurse is required to assist the patient to identify the appropriate dose on the pen and it can then be self-administered by the patient or by a carer following training. Concizumab is administered daily and is intended for ongoing long-term prophylaxis. Where bleeding is well controlled on concizumab, this could be lifelong, or until the development of drug autoantibodies or unacceptable toxicity.

Figure 1 Concizumab portable multidose disposable prefilled pens (Source: Application 1805)

According to the Australian Product Information, treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia. Treatment is to be initiated in the non-bleeding state and after discontinuing treatment with BPAs.

The recommended dosing regimen consists of an initial loading dose, followed by a standard maintenance dose (Table 5). Four weeks after initiation of treatment, trough (i.e. pre-dose) concizumab plasma concentration is measured (once) by a concizumab-specific enzyme-linked immunoassay (ELISA). The results of this test are used to determine an individual's maintenance dose according to Table 6. If concizumab treatment is discontinued the patient can restart concizumab treatment on the same maintenance dose.

Table 5 Concizumab dosing regime

Treatment day	Dose phase	Concizumab dose
Day 1	Loading dose	1mg/kg once
Day 2 to >4 weeks and <8 weeks	Initial maintenance dose	0.20 mg/kg per day
From determination onwards	Maintenance dose	Set individually based on Table 6

Source: MSAC Application 1805

Table 6 Determination of individual maintenance dose

Concizumab plasma concentration	Individual maintenance dose (one daily, subcutaneous)
<200 ng/mL	0.25 mg/kg
200−4000 ng/mL	0.20 mg/kg
>4000 ng/mL	0.15 mg/kg

Source: MSAC Application 1805

The applicant reported that the test used in the pivotal trial is the same as the test that is proposed in the application and that the turn-around time is around a week, with a 10-day turn-around guaranteed (pre-PASC meeting, 27 June 2025). In the trial, of the 97 patients who had their concizumab plasma concentration measured:

- 72 (74%) continued with a maintenance dose of 0.2 mg/kg;
- 24 (25%) had their dose increased to 0.25 mg/kg; and
- 1 (1%) had their dose reduced to 0.15 mg/kg (Matsushita et al. 2023).

The dose of concizumab is not adjusted if a breakthrough bleed occurs and BPAs are used, with their dose and duration based on the location and severity of the bleed. Therefore, the intervention includes the use of BPAs, usually rFVIIa for cHMB, for on demand treatment. The BPA would be used concomitantly with concizumab.

Registration status of the drug

Concizumab was approved by the TGA in July 2023 and is indicated where prophylaxis is required to prevent or reduce the frequency of bleeding in patients at least 12 years of age who have:

- HMB (congenital FIX deficiency) with FIX inhibitors
- HMA (congenital FVIII deficiency) with FVIII inhibitors

In January 2025, concizumab was further approved by the TGA for:

- HMB (congenital FIX deficiency) without FIX inhibitors
- HMA (congenital FVIII deficiency) without FVIII inhibitors.

The population considered in this PICO Confirmation is cHMB with inhibitors only and therefore is narrower than the TGA-indicated population.

Concizumab is subject to additional monitoring by the TGA (black triangle) including the provision of periodic safety update reports (PSURs). It has received approval in a number of other jurisdictions including Canada, the EU and the USA.

PASC accepted the intervention of prophylaxis with concizumab and on demand treatment with BPAs.

PASC considered that given the applicant's proposed removal of the population requiring short-term peri-operative prophylaxis from the proposed population, the wording of the proposed intervention 'Ongoing prophylaxis with concizumab (Alhemo®) plus/minus on demand bypassing agents (BPAs) to treat bleeds, or short-term perioperative prophylaxis with concizumab +/- on demand BPA' should be amended to remove the reference to short-term perioperative prophylaxis.

Registration status of the concizumab dose-setting test

The ConcizuTrace™ ELISA was approved by the TGA in October 2024 (ARTG 466665) for determining the concentration of the drug, concizumab, in plasma from patients with cHMA and cHMB. However, due to the small Australian patient population, the test will be conducted overseas.

The TGA noted that in vitro diagnostics that are intended to be used to monitor treatment with a therapeutic drug are generally not considered companion diagnostics, but that the test proposed for concizumab dose setting is novel and not established and therefore of adequate risk level to be considered within the TGA's companion diagnostic framework. The Advisory Committee on Medicines (ACM) was asked to consider whether a second dose adjustment step based on a repeat serum trough level should be

recommended. The ACM did not recommend this but did note that free availability of post-market testing of concizumab levels would be valuable to allow data collection (TGA, 2024).

According to Technical Guidance 15.6 of the MSAC Guidelines, "health technologies are codependent when the patient health outcomes related to the use of a therapeutic health technology (e.g. a medicine) are improved by the use of another health technology (e.g. an investigative technology)." Based on this definition, the ConcizuTrace ELISA dose optimisation test and concizumab may be considered codependent as the Guidelines recognize a "monitoring test to determine specific therapeutic management or medicine dose" as a type of codependent technology. However, the ConcizuTrace ELISA is the same as that used in the pivotal explorer7 trial, which established the clinical utility of the test-treatment combination (the clinical utility standard). Most patients did not undergo a dose adjustment (change in management) following testing (Matsushita et al. 2023). Given the very small patient population, the current PICO criteria developed did not explicitly identify the ELISA dose optimisation test as a codependent test for assessment, nor include test performance outcomes in the proposed PICO set.

The applicant confirmed that the concizumab dose-setting test will be conducted overseas at a laboratory in Japan, and that this arrangement is unlikely to change if the population is expanded to include all patients with cHMB. The clinical expert stated that the drug levels are very stable, with only 1 patient requiring a dose adjustment, which may require a second test. PASC noted that the concizumab dose-setting test does not need to be assessed as a co-dependent technology but has requested information on the ELISA assay to be included in the assessment.

Registration status of the anti-concizumab antibody test

Formation of anti-drug antibodies (ADAs) is a known consequence of monoclonal antibody treatment, although they do not necessarily prevent therapeutic monoclonal antibody activity. Anti-concizumab antibody testing was undertaken during the explorer7 trial. Antibodies to concizumab were detected in 33/127 patients (26%); all but 1 had low antibody titres and no effect on efficacy was observed (Matsushita et al. 2023).

Anti-concizumab antibody testing during the trial was undertaken by the sponsor using a bridging electrochemiluminescense assay with positive samples further tested for neutralising activity. The trial protocol notes that patients positive for binding antibodies may be followed up outside of the trial protocol (Matsushita et al. 2023). The anti-concizumab antibody tests are not commercially available and therefore not TGA registered. The applicant advised that testing is not proposed to be undertaken routinely but could be considered where a patient experiences lack of efficacy.

ADA testing is not considered a codependent test for this assessment, nor was it considered in Application 1510.1 (emicizumab). It differs from the anti-AAV5 neutralising antibody that was codependent for Application 1728.1 (Hemgenix), where testing was required to determine eligibility for the treatment due to prior exposure to the viral vector for the drug.

The applicant confirmed that there is no commercial assay for the ADA test and that this is also the case for emicizumab. The clinical expert noted that approximately 700 patients are currently treated with emicizumab, and no issues related to neutralising antibodies have been observed. Therefore, routine testing is not necessary and need not be included as part of the intervention.

Comparator(s)

There are no long-term prophylactic treatments available for patients with cHMB with inhibitors. The proposed comparator is standard of care, which consists of

- on demand treatment with BPAs, most commonly rFVIIa
- short-term prophylaxis for up to 3 months with rFVIIa.

The comparator in the explorer7 pivotal trial was on demand treatment with BPAs (Matsushita et al. 2023); however, rFVIIa is also indicated for surgical prophylaxis and short-term prophylaxis in patients with high bleeding frequency.

PASC confirmed the comparator.

Outcomes

The outcomes relevant to the assessment are listed below.

Safety

- Incidence and severity of adverse events
    - Thrombosis
- Mortality
- Emergence of anti-concizumab antibodies

Effectiveness

- Primary effectiveness
    - Reduction in number of bleeds over time (bleed rate)
    - Prevention of bleeds
- Secondary effectiveness
    - Responder status
    - Other bleeding related outcomes such as: number of joint bleeds over time; number of target joint bleeds over time; individual bleed rate compared to historical bleed rate; and number of treated bleeds per month or year.
    - Perioperative use of therapy and outcomes
    - Health-related quality of life
    - Joint health outcomes
    - Chronic pain associated with haemophilia
    - Number of missed days of work/activity/school

Healthcare resources

- Cost offsets (including costs of immune tolerance therapy)
- Costs of delivering the intervention
- Costs of managing adverse events or breakthrough bleeding
- Cost per quality-adjusted life year (QALY) gained.

The outcomes are consistent with those proposed in the application and Application 1510.1 (emicizumab). Furthermore, the primary outcome of the explorer7 pivotal trial is the same as the proposed primary effectiveness outcome. The trial also reported adverse events and health-related quality of life (Matsushita et al. 2023).

The development of anti-concizumab antibodies was not an outcome proposed in the application but has been proposed as an additional outcome by the assessment group.

PASC requested that thrombosis be specified as a separate safety outcome rather than grouped under adverse events. The clinical expert noted that thrombosis occurs in patients with mild cHMB.

PASC also agreed to retain the emergence of anti-drug antibodies (ADAs) as a safety outcome.

PASC noted that 'perioperative use of therapy and outcomes' should still be included as an outcome, even though the population requiring short-term peri-operative prophylaxis was removed from the proposed population. Collecting data on short-term perioperative outcomes is important to ensure a comprehensive evaluation and to support the safe clinical use of concizumab.

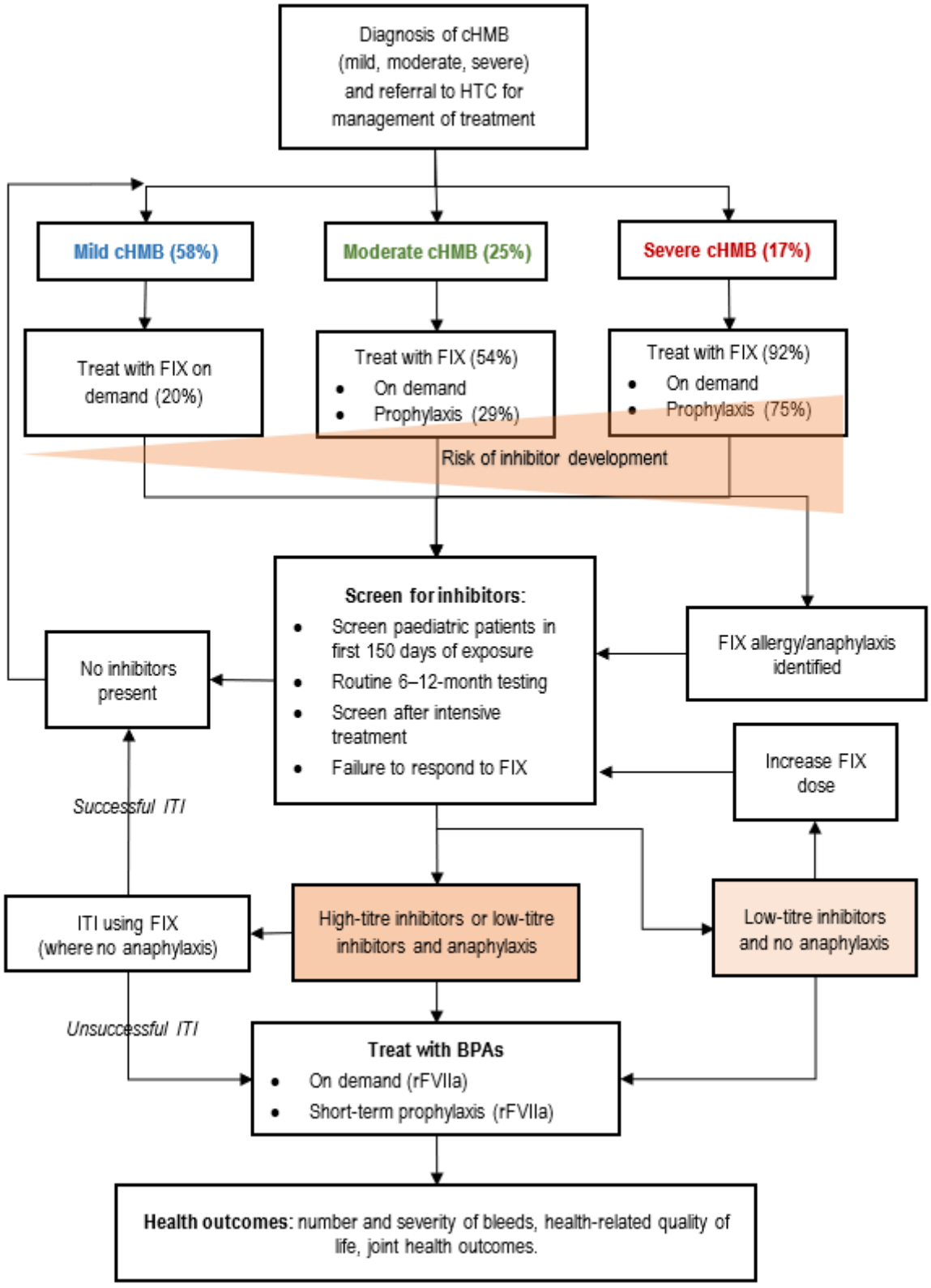
Clinical management algorithms

Current and proposed clinical management algorithms for cHMB with inhibitors are provided in Figure 2 and Figure 3. Current treatment is guided by disease severity. This is measured by FIX activity but there is also individual variation in bleeding phenotype, patient preferences and patient circumstances. The development of FIX inhibitors is almost exclusively seen in patients with severe cHMB, but rare patients with milder disease are not explicitly excluded from the proposed treatment. Patients are screened for inhibitors during their initial exposure to endogenous FIX, following intensive treatment, at routine intervals, and whenever there is a reduced effectiveness of FIX.

For patients with cHMB and low tire inhibitors and no anaphylaxis, higher doses of FIX may be used to manage bleeds. For high titre inhibitors and patients with anaphylaxis, ITI may be attempted; however, it has a low success rate and is not a mainstay of treatment. The BPA rFIIVa is used to manage bleeds and is approved for short-term prophylaxis (up to 3 months); however, there is no long-term prophylactic treatment available. These patients are therefore at risk of poor disease outcomes and have high unmet needs.

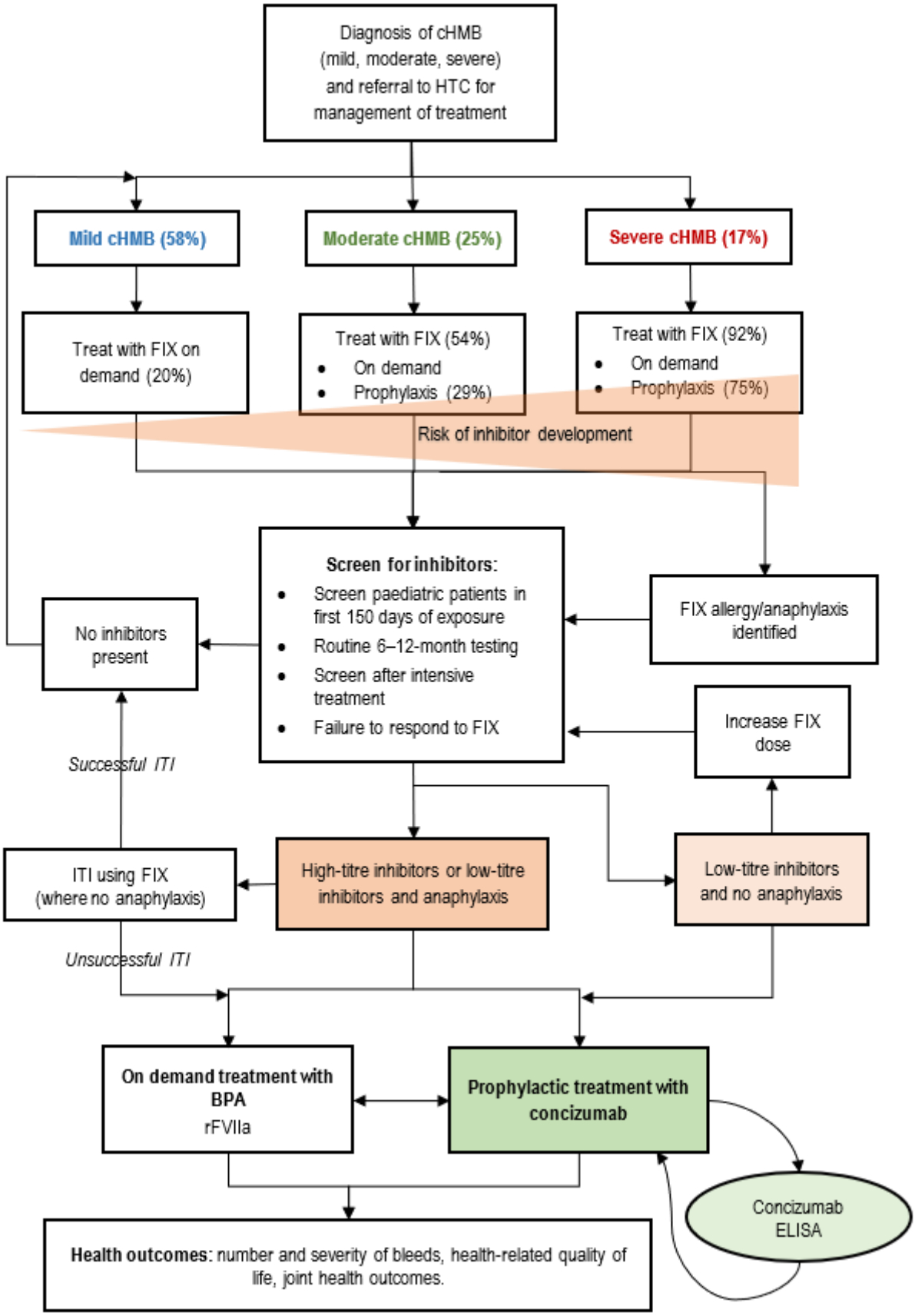
Concizumab is proposed to provide an option for long-term prophylaxis for people with cHMB with inhibitors leading to reduced bleed frequency and improved disease outcomes and quality of life. It will replace the use of short-term prophylaxis with rFVIIa but will not replace on demand use for bleeding episodes.

Figure 2 Current clinical management pathway for patients with congenital Haemophilia B and inhibitors



Source: prepared by assessment group based on MSAC Application 1805, ratified PICO Confirmation 1510, and data from the ABDR annual reports.
aPCC = activated prothrombin complex concentrate, BPA = bypassing agent, cHMB = congenital Haemophilia B, FIX = Factor IX, HTC = haemophilia treatment centre, ITI = immune tolerance induction, rFVIIa = recombinant Factor VIIa.

Figure 3 Proposed clinical management pathway for patients with congenital Haemophilia B and inhibitors



Source: prepared by assessment group based on MSAC Application 1805, ratified PICO Confirmation 1510, and data from the ABDR annual reports.
aPCC = activated prothrombin complex concentrate, BPA = bypassing agent, cHMB = congenital Haemophilia B, ELISA = enzyme linked immunoassay, FIX = Factor IX, HTC = haemophilia treatment centre, ITI = immune tolerance induction, rFVIIa = recombinant Factor VIIa.

PASC agreed with the clinical management algorithm.

Proposed economic evaluation

Based on the application's claim of **superior effectiveness** (in terms of reduced bleeds) and **non-inferior safety** (in terms of adverse events), a cost-utility analysis (CUA) is appropriate (Table 7).

However, the analysis may be hampered by the fact that the cost-effectiveness of the comparator (BPAs) has not been established and MSAC previously considered that they had a high price per patient. In the Public Summary Document for Application 1510.1 (emicizumab) MSAC noted that:

> "cost-effectiveness studies have never been used to inform the existing prices for BPAs, making economic evaluations difficult for applications such as this which rely on accepting that BPAs are acceptably cost-effective. MSAC wondered if it would be informative to commission a study to identify the reduction in prices at which BPAs would be acceptably cost-effective, especially since there are products on the horizon that are similar to emicizumab, and that would likely be put forward for public funding in the future."

Given these concerns, PASC advice is sought on whether an alternative approach to the economic evaluation might be appropriate. In the assessment of emicizumab, the department outlined two options: the first was a review of BPAs, but this was considered resource intensive; and uncertain, and the second was a pricing reduction.

The key evidence cited in the application to support the clinical claims is the explorer7 pivotal trial. The explorer7 trial was a sponsor-designed, prospective, multicenter, open-label, phase 3a randomised controlled trial that compared concizumab prophylaxis with no prophylaxis in patients with cHMA (n=80) and cHMB (n=53) with inhibitors. Patients had to have been treated with, or received a prescription of, BPAs in the 24 weeks before screening. The trial included 2 randomised groups allocated 2:1 to concizumab prophylaxis versus on demand treatment with BPAs. An additional 2 non-randomised groups were also included in the trial, all of whom received concizumab prophylaxis. In total, 133 patients were enrolled. Of the randomised patients, 33 received concizumab (for at least 32 weeks) and 19 received no prophylaxis (for at least 24 weeks). The primary outcome was treated spontaneous and traumatic bleeding episodes. Safety, patient reported outcomes, pharmacokinetics and pharmacodynamics were also assessed (Matsushita et al. 2023). No long-term data are available and the number of patients with cHMB in the study is small.

The trial included a treatment pause due to three patients experiencing nonfatal thromboembolic events. Following the treatment pause, the trial was restarted and included updated guidance for the management of breakthrough bleeding and the establishment of the dosing regimen that includes dose adjustment following testing of plasma concizumab levels (Matsushita et al. 2023).

Table 7 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain[a]	Noninferior[b]	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis.
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis.
[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations.
[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence.

PASC noted that the economic evaluation is complicated by the lack of an established cost-effectiveness for the comparator. PASC requested clarification on the proposed economic evaluation based on the applicant's pre-PASC response. The applicant proposed to undertake an approach similar to that used in Application 1510 (emicizumab), described as a cost-consequence analysis, but essentially a cost minimisation analysis that takes into account the reduced bleeding rates associated with concizumab. The main cost driver will be on-demand treatment with rFVIIa. PASC noted that this approach assumes no cost difference in any other aspects of treatment. PASC advised that this assumption must be explicitly stated in the ADAR and supported with appropriate justification.

PASC also advised the department to consider establishing the cost effectiveness of BPAs. The current approach involves cost-minimising concizumab against BPAs and other newer agents, all of which have been cost-minimised against each other without a clear, established cost-effectiveness benchmark. PASC raised concerns that BPAs such as rFVIIa are very expensive, which challenges the validity of the cost-minimisation approach.

Proposal for public funding

Concizumab

Funding is proposed via the National Blood Agreement. No MBS item descriptor is required for the application.

The application states that concizumab will be cost-minimised on an annualised basis to the comparator, rFVIIa, and therefore will be cost-neutral. A chart review is proposed to record actual usage of rFVIIa over time in the Australian patients with cHMB with inhibitors. In addition, the applicant proposes to provide rFVIIa at no cost for treatment of breakthrough bleeds for patients on concizumab prophylaxis.

Concizumab ELISA test

The application proposed that blood collection for the concizumab-ELISA test will be covered under MBS item 66812 which currently exists for quantitation, by any method or methods, in blood, urine or other body fluid, of a drug being used therapeutically by the patient from whom the specimen was taken. However, as the test is to be undertaken outside of Australia, the department advised that there is no MBS item that can be used to cover only a part of the pathology service rendered (e.g. blood collection component). Therefore, no Medicare rebate will apply.

The application states that Novo Nordisk intends to cover all costs associated with the concizumab-ELISA assay. The pathology service will also need to be covered by the sponsor, or the HTC, given it is not eligible for a Medicare rebate, otherwise patients could be left with out-of-pocket expenses.

Regarding the concizumab ELISA test, the applicant stated that the HTC will pay for the blood draw and the onsite processing of the sample (centrifugation, freezing etc). The applicant will cover the costs of collecting the sample and sending it to the centralised lab for testing.

Summary of public consultation input

PASC noted and welcomed consultation input from 4 organisations, the organisations that submitted input were:

- Australian Haemophilia Centre Directors' Organisation (AHCDO)
- Haemophilia Foundation Australia (HFA)
- Public Pathology Australia (PPA)
- Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ).

Consultation input was supportive of public funding for concizumab for routine prophylaxis to prevent bleeding in patients with cHMB.

Consumer input

HFA input included consumer experiences, and stated that living with cHMB and FIX inhibitors was usually debilitating and sometimes caused death, due to uncontrolled bleeding. Input stated that people with cHMB and FIX inhibitors live with significant pain, have poor mobility, are often wheelchair bound, depend on pain relief and miss out on daily activities. Missing out on social functions, team sports and travel with family and friends due to the effects of uncontrolled bleeding had an ongoing negative impact on relationships, social connection and mental health.

Benefits and disadvantages

The main benefits of public funding reported in the consultation input included a prophylactic option for treatment, subcutaneous delivery rather than venous infusions, reduction in bleeding, and improved quality of life. HFA input from health professionals and people who had accessed concizumab through clinical trials stated that the pen device is easy to use, the liquid can be stored at room temperature, treatment is less painful, and bleeding episodes were greatly reduced.

There were no disadvantages of public funding identified in the consultation input.

Population, comparator (current management) and delivery

The consultation input agreed with the proposed population, with all organisations stating that people with cHMB and FIX inhibitors are a very rare group, with no prophylactic therapy currently available and have the greatest unmet need within the population of patients with haemophilia. AHCDO noted that clinical trials included people with cHMA (with and without FVIII inhibitors) and people with cHMB (with and without FIX inhibitors) and that all people with haemophilia could benefit from concizumab. However, AHCDO acknowledged the subpopulation proposed has the greatest unmet need and was appropriate.

The consultation input agreed with the proposed comparators, noting that standard of care is BPAs as there are no approved and funded prophylactic treatment options for people with cHMB and FIX inhibitors.

The consultation input stated that people with haemophilia can access expert medical care, nursing, counselling, physiotherapy, data management and laboratory services through the HTC comprehensive care team.

Additional Comments

Consultation input noted that there would be no out-of-pocket costs for patients, as approved products are funded through the NBA and the applicant would cover the costs for pathology testing.

PPA noted that there are no laboratories in Australia able to provide the trough plasma concizumab concentration assay, and that concizumab targets the tissue factor pathway in ways that cannot currently be monitored. Should monitoring of TFPI inhibitors become required, new assays may need to be set up.

PASC noted the feedback was generally supportive, highlighting the need for treatment in patients with cHMB and FIX inhibitors, who often experience debilitating symptoms. PASC also noted feedback indicating that subcutaneous delivery, rather than intravenous infusions of prophylactics, would improve both equity and quality of care for patients with cHMB and FIX inhibitors.

Next steps

The applicant confirmed that the assessment will proceed as an applicant-developed assessment report (ADAR). The applicant will consider PASC's advice to broaden the population to align with the TGA-approved indications for the cHMB population.

Applicant Comments on Ratified PICO

The applicant will submit an ADAR to align with the TGA-approved indications for the cHMB population.

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