MSAC Application 1805

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

PICO Set

Population

Describe the population in which the proposed health technology is intended to be used:

This application is for the funding of concizumab for the prophylactic treatment of patients with Haemophilia B who have developed Factor IX inhibitors (HMBwI).

Haemophilia B (HMB) is a chronic bleeding disorder caused by deficiency or dysfunction of the coagulation protein Factor IX (FIX) (Dolan, Benson et al. 2018, Kizilocak and Young 2019, Samuelson Bannow, Recht et al. 2019). HMB is a serious and life-threatening condition in which patients experience spontaneous, painful bleeding episodes and prolonged, excessive haemorrhage following trauma or surgery (Llinás, Poonnoose et al. 2020, Mahlangu, Dolan et al. 2020, Santagostino, Dougall et al. 2020). HMB is also associated with severe joint disease, disability and poor health related quality of life (HRQoL) (Hartl, Reitter et al. 2008, Holstein, von Mackensen et al. 2016, O'Hara, Walsh et al. 2018, Kizilocak and Young 2019, Butterfield, Hege et al. 2020, Llinás, Poonnoose et al. 2020, Mahlangu, Dolan et al. 2020, Santagostino, Dougall et al. 2020). This crippling joint disease and disability is contributed to by bleeding into joints (haemarthrosis). Haemarthrosis is the hallmark of the severe phenotype, accounting for 70%–80% of all bleeding episodes (Kizilocak and Young 2019, Butterfield, Hege et al. 2020). If left untreated, HMB leads to significant morbidity and reduced life expectancy. The mainstay of treatment involves the intravenous (iv) infusion of plasma-derived or recombinant FIX on demand (when a bleed occurs) or as part of a long-term prophylaxis regimen (AHCDO 2016).

The development of neutralising anti-FIX antibodies (inhibitors) against exogenous clotting factor replacement therapy is one of the most serious and challenging complications of haemophilia, occurring in approximately 1—6% of HMB patients (Lai, Hough et al. 2017, Lai and Lillicrap 2017, Peyvandi, Ettingshausen et al. 2017, Giangrande, Hermans et al. 2018, National Hemophilia Foundation 2018). According to the ABDR 2021/22 report, there are <5 patients diagnosed with HMBwI in Australia (National Blood Authority 2021), REDACTED.

The presence of circulating inhibitors partially or completely inactivates infused factor proteins, impairing their clinical efficacy and making the management of bleeding exceedingly difficult (Ragni 2017, Miller 2018). As a result, patients with HMBwI experience significant reductions in their HRQoL and pose an increased economic burden on healthcare systems (D'Angiolella, Cortesi et al. 2018, Oladapo, Lu et al. 2018, Ragni, Berntorp et al. 2020).

Strategies for optimal care for individuals with HMBwI may include:

- Active bleeding and perioperative management most commonly on demand (when a bleed occurs), and occasionally as part of a short-term prophylactic regimen (administered as a once daily dose for up to three months) with an iv bypassing agent (BPA). NovoSeven® RT (recombinant coagulation factor VIIa (rFVIIa)) is the most commonly utilised BPA by HMBwI patients (National Blood Authority 2021).
- Inhibitor eradication — Inhibitor eradication using immune tolerance induction (ITI) is appropriate for individuals with high-titre inhibitors or high-responding individuals, as well as individuals with low-titre inhibitors. ITI is not the mainstay of HMBwI treatment in Australia as it is a demanding and resource-heavy treatment that is only successful in a small proportion of patients. The World Federation of Haemophilia (WFH) guidelines note the low success rate in HMBwI patients (approximately 70% of HMBwI patients fail to respond to ITI) (Wight, Paisley et al. 2003, Kempton and Meeks 2014) and therefore are unable to make a recommendation on the use of ITI in the HMBwI population (Ragni, Berntorp et al. 2020).
- Importantly, unlike Haemophilia A patients, there is significant unmet need in HMBwI as there have been **no long-term prophylaxis treatment options available**
- Concizumab represents the **first and only long-term prophylaxis treatment approved for HMBwI**

Optimal management of patients with HMBwI is highly nuanced and patient specific, specialised and multidisciplinary in nature. Various detailed clinical guidelines are available both locally (AHCDO 2016) and internationally (Giangrande, Hermans et al. 2018, Hermans, Giangrande et al. 2020, Ragni, Berntorp et al. 2020), which summarise a constantly evolving treatment landscape and evidence base. In Australia people living with HMBwI receive care through dedicated HTCs.

Patients with HMB that have developed inhibitors to FIX face a number of additional challenges in the management of their disease (Hermans, Giangrande et al. 2020):

1. There have been no long-term prophylaxis treatments approved for HMBwI, despite the widely established benefits of prophylaxis in reducing bleed rates and slowing disease progression (Royal, Schramm et al. 2002, Hoots and Nugent 2006, Collins, Faradji et al. 2010,

Iorio, Marchesini et al. 2011, Manco-Johnson, Soucie et al. 2017, Castaman 2018, Miesbach, Kittler et al. 2020).

i. The WFH currently has no recommendation on prophylaxis in HMBwI due to a lack of efficacious and safe treatment options (Ragni, Berntorp et al. 2020).

ii. NovoSeven® RT (rFVIIa) is the only recombinant BPA currently approved for on demand treatment in HMBwI patients and short-term prophylaxis (up to 3 months). Treatment of patients with HMBwI may be complicated further by the risk of severe allergic reactions to infused FIX (Chitlur, Warrier et al. 2009). The alternative plasma-derived BPA approved for prophylactic and on demand use in HMBwI patients, Feiba®, may be used however, guidelines suggest it be avoided as it contains FIX and may trigger an anamnestic response (National Hemophilia Foundation 2018, Ragni, Berntorp et al. 2020).

iii. ITI is associated with poor clinical response in patients with HMBwI (Shapiro, Angchaisuksiri et al. 2019), with experts agreeing that research is needed to find alternatives to ITI therapy that offer durable and sustained effects and reduced rates of complications for this population (Benson, Auerswald et al. 2012).

iv. Concizumab represents the first and only long-term prophylaxis treatment approved for HMBwI.

2. There are no available treatments with a convenient route of administration for patients with HMBwI. NovoSeven® RT is currently approved for short-term prophylaxis and requires daily iv infusions (NovoSeven® RT Product Information 2013), which is a major inconvenience for patients and their caregivers (Castaman and Linari 2018). Additionally, frequent iv injections in the prophylactic setting can cause complications due to venous access issues, pain, discomfort or anxiety (Santagostino, Dougall et al. 2020).

The lack of safe and effective long-term prophylaxis treatment options for HMBwI means that patients currently experience a significantly greater clinical and humanistic burden, compared with patients with HMB without inhibitors or patients with Haemophilia A with or without inhibitors (Morfini, Haya et al. 2007, Eckhardt, Loomans et al. 2015, Walsh, Jiménez-Yuste et al. 2016, Oladapo, Lu et al. 2018). The management of HMBwI patients also incurs substantially greater direct and

indirect costs on patients and the healthcare system, increasing the economic burden of disease (Guh, Grosse et al. 2012, Chen 2016, D'Angiolella, Cortesi et al. 2018).

New treatments that can address the unmet needs of patients with HMBwI are required to improve patient and clinical outcomes; ultimately improving humanistic and economic burdens resulting from HMBwI. In a survey of adherence to haemophilia therapy which interviewed patients across six European countries, patients' suggestions for how adherence could be improved included improved forms of administration, and more convenient storage (De Moerloose, Urbancik et al. 2008). An updated Haemophilia Treatment Preferences Survey (HaemPref Survey) conducted in partnership with the Haemiphilia Foundation Australia (HFA) found subcutaneous injections are preferred by the Australian haemophilia community (Community and Patient Preference Research, 2024).

The limitations associated with current treatment options in HMBwI highlight the potential benefits of the availability of an effective long-term prophylactic treatment with a minimally invasive route of administration, which can be used concomitantly with on demand treatments without additional safety concerns.

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed, and referred within the Australian health care system in the lead up to being considered eligible for the technology:

HMBwI patients experience a significant reduction in health outcomes including higher levels of pain and physical burden compared to patients without inhibitors and reduced HRQoL as a result of limited treatment options (Morfini, Haya et al. 2007, Oladapo, Lu et al. 2018). Considering the unmet needs of these patients, the proposed population eligible for routine prophylaxis with concizumab identified in this PICO set are patients diagnosed with HMBwI.

Patients with a confirmed diagnosis of HMBwI would currently be receiving care through one of the specialist Australian HTCs although the investigative, management and referral pathways leading to these treatment destinations are likely heterogenous. It is anticipated the assessment of suitability for concizumab would be exclusively conducted within an established HTC setting and with existing patients.

According to the ABDR 2021/22 report, there are <5 patients diagnosed with HMBwI in Australia (National Blood Authority 2021). No further tests to quantify or diagnose these patients will be required. As mentioned previously, the submission assumes there are four patients with HMBwI in Australia based on feedback from HTCs. An overview of how HMB is diagnosed and how the presence of inhibitors is confirmed is provided below for contextual purposes.

The guidelines for the management of haemophilia in Australia suggest the following diagnostic methods for diagnosing Haemophilia B patients and confirming the presence of inhibitors (AHCDO 2016).

Diagnosis of Haemophilia: History

Haemophilia should be suspected in patients presenting with a history of (AHCDO 2016):

- Easy bruising in early childhood
- 'Spontaneous' bleeding (i.e., bleeding for no apparent or known reason, or due to minor trauma not identified by the patient), particularly into the joints, muscles and soft tissues
- Excessive bleeding following trauma or surgery
- Primary menorrhagia and postpartum bleeding (in affected females)

Although a family history of bleeding is present in about two-thirds of all patients with haemophilia (AHCDO 2016), a negative family history cannot be used as evidence against a haemophilia diagnosis as many cases are sporadic (W Keith Hoots 2022).

Weight-bearing joints and other joints are principal sites of bleeding in patients with haemophilia. The muscles most commonly affected are the flexor groups of the arms and gastrocnemius of the legs.

The diagnostic evaluation in cases of suspected haemophilia typically begins with a thorough review of the patient's personal bleeding history and family history. Screening tests are then performed, and the diagnosis is confirmed with a specific clotting factor activity measurement(s) and/or genetic testing (W Keith Hoots 2022).

Diagnosis of Haemophilia (including Inhibitors): Laboratory Testing

Diagnosis of haemophilia is based on the following three principles:

1. Understanding the clinical features of haemophilia and the appropriateness of the clinical diagnosis.

2. Using screening tests such as prothrombin time (PT) and activated partial thromboplastin time (APTT) or platelet function tests to identify the potential cause of bleeding (keeping in mind that normal screening test results do not exclude the possibility of a clinically relevant bleeding disorder being present); and
3. Confirming the diagnosis by factor assays and other appropriate specific investigations.

The following laboratory diagnostic tests are used in Australia to diagnose haemophilia and differentiate inhibitor and carrier status.

Table 1 Investigative Tests to confirm Haemophilia B diagnosis.

Investigative Tests	Relevant Notes
<u>Initial evaluation</u> • Full blood count • APPT • PT • International normalised ratio	There is an isolated prolongation of the APTT in severe and moderate haemophilia; the test may not be sufficiently sensitive to detect those with mild haemophilia, with Factor VIII or IX levels >30%
<u>Diagnosis of Haemophilia B</u> • Plasma (FIX) assay	A definitive diagnosis depends on a laboratory assay result that demonstrates a deficiency in FIX
<u>Development of inhibitors</u> • Coagulation factor inhibitors test	Test based on the inability of normal plasma to correct prolonged APTT (or PT). Further testing is required for quantifying inhibitor levels.
<u>Quantification of inhibitor</u> • Bethesda assay	Inhibitors may be low or high-titre; A low-responding inhibitor is defined as an inhibitor level that is persistently below 5 Bethesda units (BU)/ml, whereas a high-responding inhibitor is defined by a level of at least 5 BU/m
<u>Carrier diagnosis</u> • Patient and family history • Plasma (FIX) assay • von Willebrand factor antigen • DNA analysis	Some carriers have completely normal coagulation results, and the possibility of a carrier state cannot be excluded on these assays. Molecular genetics testing increases the detection rate, but a definitive answer cannot always be obtained.

Source: (AHCDO 2016)

Abbreviations: APTT, Activated partial thromboplastin time; Bethesda units, BU; DNA, deoxyribonucleic acid; FIX, Factor IX; PT, Prothrombin time.

In all cases, inhibitors render effective treatment with replacement factor concentrates difficult or not possible. Patients on clotting factor therapy should therefore be followed for the possible development of inhibitors and screened as required (AHCDO 2016).

Confirmation of the presence of an inhibitor and quantification of the titre is performed in the laboratory, preferably using the Nijmegen-modified Bethesda assay. For children, inhibitors should be screened 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 factor concentrate replacement therapy in a previously responsive patient is an indication to assess for an inhibitor (AHCDO 2016).

Provide a rationale for the specifics of the eligible population:

The rationale for the patient population is based on the investigative population in the Explorer7 trial. The Explorer7 trial demonstrated superior clinical outcomes in HMBwI patients treated with concizumab prophylaxis compared to patients given on demand treatment with bypassing agents (Matsushita, Shapiro et al. 2023).

Concizumab is an anti-tissue factor pathway inhibitor (TFPI) antibody which can be administered subcutaneously as prophylaxis therapy for patients with HMBwI. Concizumab acts independently from Factor VIII (FVIII) and Factor IX (FIX) by enhancing the initiation phase of coagulation through increased activated Factor X (FXa) production.

Concizumab has been approved by the Therapeutic Goods Administration (TGA) 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 (Alhemo® Product Information 2023):

- Haemophilia B (congenital FIX) with FIX inhibitors
- Haemophilia A (congenital FVIII) with FVIII inhibitors

Concizumab was further approved by the TGA in January 2025 for the below indications:

- Haemophilia B (congenital FIX) without FIX inhibitors
- Haemophilia A (congenital FVIII) without FVIII inhibitors

Are there any prerequisite tests? (please highlight your response)

Yes **No**

Are the prerequisite tests MBS funded? (please highlight your response)

Yes **No**

Please provide details to fund the prerequisite tests:

N/A

Intervention

Name of the proposed health technology:

Concizumab (Brand name: Alhemo®)

Describe the key components and clinical steps involved in delivering the proposed health technology:

Concizumab is being studied via the Novo Nordisk Explorer clinical trial program. Based on results obtained with concizumab in HMBwI patients, the TGA granted concizumab Priority Review Determination (Therapeutic Goods Administration 2022). In July 2023, concizumab was approved by the TGA and indicated where prophylaxis is required to prevent or reduce the frequency of bleeding in patients at least 12 years of age who have inhibitors (Alhemo® Product Information 2023):

- Haemophilia B (congenital FIX) with FIX inhibitors
- Haemophilia A (congenital FVIII) with FVIII inhibitors

Concizumab was further approved by the TGA in January 2025 for the below indications:

- Haemophilia B (congenital FIX) without FIX inhibitors
- Haemophilia A (congenital FVIII) without FVIII inhibitors

Treatment should be initiated under the supervision of a physician experienced in treatment of haemophilia and/or bleeding disorders. Treatment should be initiated in a nonbleeding state.

Concizumab has the advantage of being administered subcutaneously, and exhibits good solubility and stability, allowing administration as a liquid formulation via a ready- and easy-to-use portable pen device (Figure 1). These advances both represent significant improvements over BPAs which require frequent iv bolus injections. Concizumab will be supplied as a portable, multidose, disposable, ready to administer 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).

Figure 1 Portable multidose disposable ready to administer prefilled pen.

Concizumab is recommended to be used with NovoFine® needles with a gauge of 32 and a length of 4 mm. If needles longer than 4 mm are used, injection techniques that minimise the risk of intramuscular injection should be used (Alhemo® Product Information 2025).

The anticipated recommended dosing regimen:

- Day 1: a single loading dose of 1 mg/kg
- Day 2 and until individual maintenance dose is set (see below): once daily dosing of 0.20 mg/kg
- Four weeks after initiation of treatment: measurement of concizumab predose plasma concentration (once) by a concizumab specific enzyme-linked immunoassay (ELISA)
- When the concizumab plasma concentration results are available: individual maintenance dose is set once, based on concizumab plasma concentration as indicated below in Table 2

Table 2 Individual maintenance dose based on concizumab plasma concentration for patients with HMBwI.

Concizumab plasma concentration	Once daily dose concizumab
<200 ng/mL	0.25 mg/kg
200–4000 ng/mL	0.20 mg/kg
>4000 ng/mL	0.15 mg/kg

Individual maintenance dose setting should be performed at the earliest convenience (after concizumab plasma concentration result is available) and recommended no later than eight weeks after initiation of treatment. The calculation of the concizumab dose (in mg) is shown below:

Patient body weight (kg) x dose (1, 0.15, 0.20 or 0.25 mg/kg) = total amount (mg) of concizumab to be administered.

The dose is dialled on the pen in increments of (Figure 1):

- 0.1 mg on the 15 mg/1.5 mL (10 mg/mL) (blue pen)
- 0.4 mg on the 60 mg/1.5 mL (40 mg/mL) (brown pen) and
- 1.0 mg on the 150 mg/1.5 mL (100 mg/mL) and 300 mg/3 mL (100 mg/mL) (gold pens)

The doctor or nurse must assist the patient in rounding off and identifying the appropriate injectable dose on the pen.

If concizumab treatment is discontinued the patient can restart concizumab treatment on the same maintenance dose.

Treatment with rFVIIa i.e., NovoSeven® RT should be discontinued at least 12 hours before starting concizumab therapy and treatment with activated prothrombin complex concentrate (aPCC; FEIBA) should be discontinued at least 48 hours before.

The concizumab-ELISA test is intended to quantitate the concentration of concizumab in human citrated plasma from patients. The concizumab-ELISA has been used throughout the clinical development program for measuring concizumab exposure (PK). In the Explorer clinical trial program, concizumab-ELISA was performed prior to the next scheduled administration of concizumab (Novo Nordisk 2020). The concentration of concizumab in human citrated plasma measured by this assay was used as the point of reference for dose adjustments in the phase 3 concizumab clinical trials. Samples collected specifically for dose adjustment were analysed using the concizumab-ELISA in vitro diagnostic (IVD) device. All other samples were analysed using the concizumab-ELISA.

The concizumab Product Information states that the concizumab-ELISA is to be used once, four weeks after initiation of treatment, to measure the concizumab plasma concentration prior to setting the maintenance dose (Alhemo® Product Information 2025).

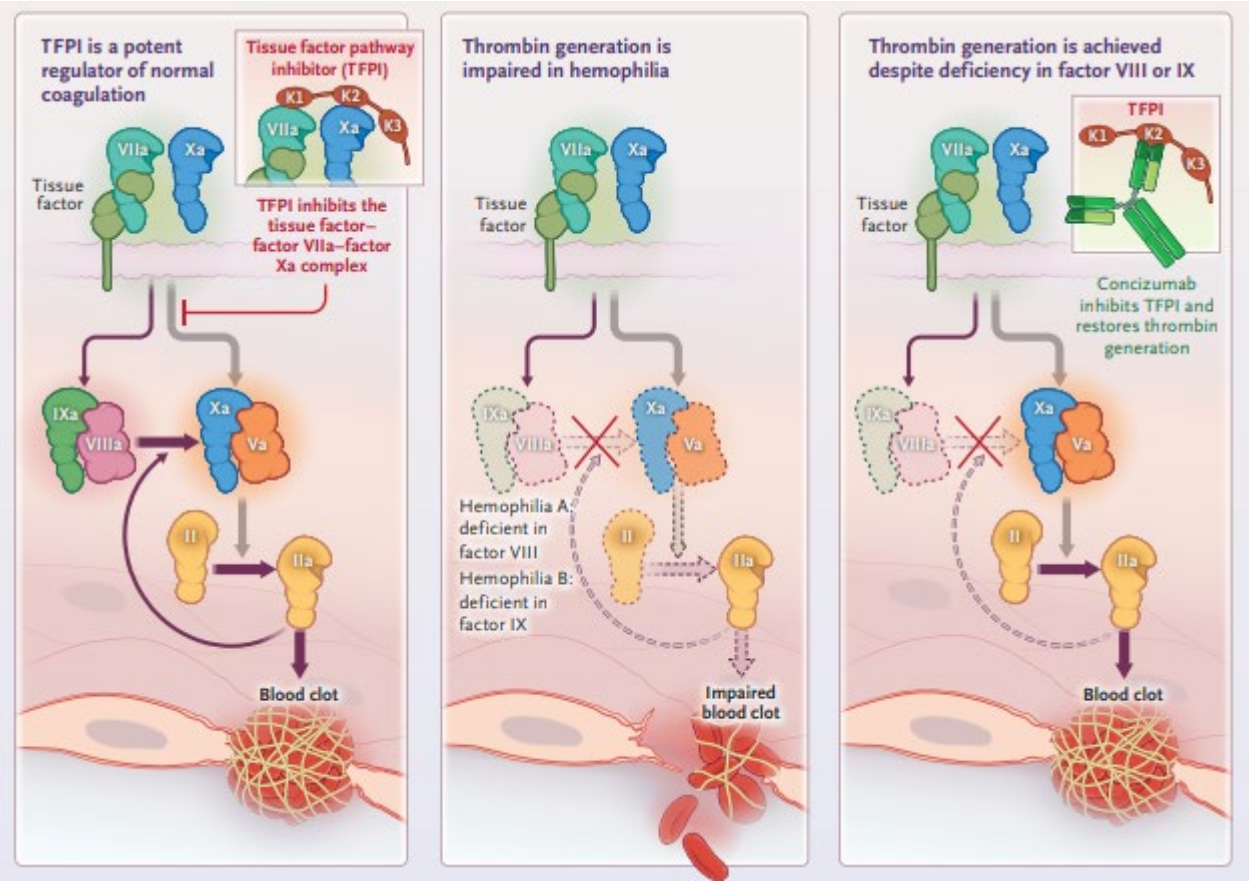
It is proposed that the blood collection for the concizumab-ELISA test will be covered under MBS item number #66812 which currently exists for quantitation, by any method or methods, in blood, urine or other body fluid, of a drug being used therapeutically by the patient from whom the specimen was taken.

Novo Nordisk intends to cover all costs associated with the actual concizumab-ELISA assay; the MBS item would cover the remaining laboratory costs ensuring patients are not left with out of pocket expenses.

Identify how the proposed technology achieves the intended patient outcomes:

Thrombin (Factor II) promotes clotting in order to re-establish haemostasis following a bleed. There are two branches in the coagulation pathway that activate thrombin (see Figure 2). The first branch involves FVIII and FIX which, once activated, generate a burst of FX, increasing thrombin formation. This branch is inactivated in people with Haemophilia A and B resulting in dysregulation of haemostasis. The second branch involves the direct activation of FX however, this process is inhibited by TFPI. TFPI is a glycoprotein that tightly regulates the initiation phase of the coagulation pathway and exists in two isoforms; TFPIα contains the Kunitz-1, -2 and -3 domains, while TFPIβ contains Kunitz-1 and -2 together with a C-terminal tail with a GPI anchor responsible for cell binding. In patients with haemophilia, concizumab binds to the Kunitz domain 2 (K2) of both TFPIα and TFPIβ inhibiting TFPI's neutralisation of FX, promoting thrombin activation, clotting and restoring haemostasis (Figure 2) (Shapiro 2021, van den Berg and Srivastava 2023).

Figure 2 Haemostasis and the mechanism of action of concizumab



Source: (van den Berg and Srivastava 2023)
Abbreviations: K1, Kunitz domain 1; K2, Kunitz domain 2; K3, Kunitz domain 3; IIa, Activated Factor II; FVIIa, Activated Factor VII; Va, Activated Factor V; VIIIa, Activated Factor VIIIa; IXa, Activated Factor IX; Xa, Activated Factor X

Concizumab is a humanised recombinant monoclonal antibody of the immunoglobulin G4 (IgG4) isotype. Concizumab is a first in class anti-TFPI antibody approved for subcutaneous, long-term prophylaxis therapy and is the only therapy approved specifically for this indication (with inhibitors) in Australia (Alhemo® Product Information 2025).

The rationale behind TFPI inhibition is that it extends the initiation phase of coagulation at sites of injury where tissue factor is exposed, thereby enhancing the remaining ability of the blood to form a clot, independent of the presence of endogenous FVIII or FIX (Shapiro 2021).

The mechanism of action of concizumab is not expected to interfere with the function of major downstream coagulation inhibitors. Therefore, concizumab is able to increase the haemostatic capacity while not interfering with downstream control mechanisms, an important attribute in terms of ensuring the appropriate function of the coagulation system in the presence of the drug (Shapiro 2021).

Concizumab acts independently from FVIII and FIX, therefore is not influenced by the presence of inhibitors to FVIII or FIX. This also ensures patients with severe allergic reactions or anaphylaxis to FIX can receive prophylactic treatment with concizumab.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components? (please highlight your response)

Yes **No**

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

N/A

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration, or frequency): (please highlight your response)

Yes No

Provide details and explain:

The efficacy and safety of concizumab in patients under the age of 12 years has not been established, therefore patients under the age of 12 years are not currently indicated to use concizumab. Explorer10 is currently exploring the effect of concizumab prophylaxis in reducing the number of bleeding episodes in paediatrics (<12 years) with HA/HB with and without inhibitors (NCT05135559). The primary data associated with use in HBwI in this population is expected to read out later in 2025.

Treatment with concizumab is contraindicated in subjects with known hypersensitivity to concizumab or any of its excipients (see Table 3 below).

Table 3 Concizumab excipients

List of excipients
• Arginine • hydrochloride • Histidine • Sodium chloride • Sucrose • Polysorbate 80

- Phenol
- Hydrochloric acid
- Sodium hydroxide
- Water for injections

Concizumab is also not indicated for treatment in the on demand setting i.e., for breakthrough bleeds. As such, HMBwl patients experiencing spontaneous or traumatic bleeding episodes would require concomitant treatment with bypassing agents approved for on demand.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

Healthcare professionals trained in concizumab administration will likely include:

- Haematologists
- Haemophilia Nurses
- Allied healthcare professionals in HTCs

These healthcare professionals may be required to administer concizumab for patients, or provide initial training, assistance in rounding off and identifying the appropriate injectable dose on the pen to the patient.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

Concizumab can be self-administered via an easy-to-use pen by the patient or administered by a carer following training by a healthcare professional.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

N/A

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology? (please highlight your response)

Yes **No**

Provide details and explain:

N/A

Indicate the proposed setting(s) in which the proposed health technology will be delivered: (select all relevant settings)

☐ Consulting rooms

☐ Day surgery centre

☐ Emergency Department

☐ Inpatient private hospital

☐ Inpatient public hospital

☐ Laboratory

☒ Outpatient clinic (Rationale: Patient receives treatment at an HTC)

☒ Patient's home (Rationale: Patient self-administers treatment in their home)

☐ Point of care testing

☐ Residential aged care facility

☐ Other (please specify)

Is the proposed health technology intended to be entirely rendered inside Australia? (please highlight your response)

Yes **No**

Please provide additional details on the proposed health technology to be rendered outside of Australia:

At the time of launch the concizumab-ELISA assay required for the one-time dose adjustment assessment, used for determining the maintenance dose, will be unavailable in Australia. Novo Nordisk will therefore arrange for samples to be sent abroad for testing at specialised facilities and cover the associated costs until the test becomes available in Australia.

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e., how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

Unlike Haemophilia A patients, there are no long-term prophylaxis treatment options available for patients with HMBwI in Australia.

The proposed comparator is standard of care, which consists of:

- Short-term prophylaxis (up to 3 months) with the bypassing agent (BPA), NovoSeven® RT (rFVIIa)
- On demand treatment with the bypassing agent (BPA), NovoSeven® RT (rFVIIa)

Use of NovoSeven® RT (rFVIIa) by patients is heterogeneous and depends on the individual requirements of the patients. For patients with a high bleeding frequency, NovoSeven® RT (rFVIIa) can be used as prophylaxis, once daily for up to three months to reduce the frequency of bleeding or can be used for surgical prophylaxis. NovoSeven® RT (rFVIIa) is otherwise used on demand in patients for the control of bleeding episodes.

Please provide a rationale for why this is a comparator:

Patients with inhibitors, particularly those with high-titre inhibitors (> 5 BU/mL), are at increased risk of uncontrollable haemorrhage, devastating joint damage and subsequent disability. For patients with low-titre inhibitors, effective management may be achieved with higher doses of FIX however, more than 80% of FIX alloantibodies are high-responding (DiMichele, Hoots et al. 2007). For these patients' use of BPAs is the primary treatment. Despite the availability of on demand and short-term prophylaxis, HMBwI patients still suffer from relatively poor clinical outcomes (D'Angiolella, Cortesi et al. 2018, Oladapo, Lu et al. 2018, Ragni, Berntorp et al. 2020).

There are currently no long-term prophylactic treatments available for patients with HMBwI as concizumab is the first and only long-term prophylaxis treatment approved for HMBwI. rFVIIa is the most appropriate comparator as patients with HMBwI currently manage bleeding episodes with on demand treatment or short-term prophylactic treatment with rFVIIa.

Concizumab will therefore replace on demand and short-term prophylactic treatment with rFVIIa (Royal, Schramm et al. 2002, Hoots and Nugent 2006, Collins, Faradji et al. 2010, Iorio, Marchesini et al. 2011, Manco-Johnson, Soucie et al. 2017, Castaman 2018, Miesbach, Kittler et al. 2020).

NovoSeven® RT Mechanism of action

The role of endogenous FVIIa in the induction of haemostasis includes the direct activation of FIX into FIXa and FX into FXa following the binding of rFVIIa to exposed tissue factor, initiating the conversion of prothrombin into thrombin. Thrombin leads to the activation of platelets, Factors V and VIII at the site of injury and the formation of a haemostatic plug by converting fibrinogen into fibrin.

Pharmacological doses of NovoSeven® RT (rFVIIa) activates FX directly on the surface of activated platelets at the local site of injury, independently of tissue factor. This results in the conversion of prothrombin into large amounts of thrombin, independent of tissue factor. Accordingly, the pharmacodynamic effect of FVIIa gives rise to an increased local formation of FXa, thrombin, and fibrin (NovoSeven® RT Product Information 2023). The Australian Haemophilia Centre Directors Organisation (AHCDO) and WFH guidelines recommend the use of NovoSeven® RT for the short-term management of bleeding patients with inhibitors (AHCDO 2016, Srivastava, Santagostino et al. 2020).

An alternative BPA approved for use in HMBwI is plasma-derived aPCC (FEIBA®) (FEIBA® Product Information 2020). rFVIIa is considered preferable for the short-term prophylactic treatment of HMBwI patients because plasma-derived aPCC contains trace amounts of FIX which could induce an anamnestic response in HMB patients with high-responding inhibitors (Srivastava, Santagostino et al. 2020).

In Australia, the only form of rFVIIa listed on the National Product List is NovoSeven® RT. NovoSeven® RT is therefore accessible for patients with HMBwI for on demand or short-term (up to 3 months) prophylactic treatment (National Blood Authority 2023).

Table 4 provides usage data on prophylactic treatments used by HMBwI patients. NovoSeven® RT and FEIBA® were the only BPAs used for prophylaxis in patients with HMBwI recently however there was no reported usage of FEIBA® in 2020-21 or 2021-22 and NovoSeven® RT is considered the preferred treatment and is therefore considered the primary comparator.

This data is derived from the 2019-20, 2020-2021 and 2021-22 ABDR reports; however, is not expected to capture actual usage of NovoSeven. A chart review will be conducted by Novo Nordisk to record actual usage of Novo Seven over time, REDACTED.

Table 4 Prophylactic product usage in patients with HMBwI

Product	**No. of patients 2019/20**	**Total units 2019/20**	**No. of patients 2020/21**	**Total units 2020/21**	**No. of patients 2021/22**	**Total units 2021/22**
NovoSeven® RT	<5	5,444	<5	2,360	<5	964
FEIBA®	<5	130,000	N/A	N/A	N/A	N/A

Source: (National Blood Authority 2020, National Blood Authority 2021, National Blood Authority 2022)
Note: Excludes average 36mg of NovoSeven® RT per year used in paediatric patients.

List any existing MBS item numbers that are relevant for the nominated comparators:

N/A

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator? (please select your response)

☐ None – used with the comparator

☐ Displaced – comparator will likely be used following the proposed technology in some patients

☒ Partial – in some cases, the proposed technology will replace the use of the comparator, but not in all cases

☐ Full – subjects who receive the proposed intervention will not receive the comparator

Please outline and explain the extent to which the current comparator is expected to be substituted:

REDACTED. According to the ABDR, there are currently <5 patients diagnosed with HMBwI in Australia. REDACTED.

Concizumab will be used as a long-term prophylaxis treatment for HMBwI with the goal of preventing bleeding, while allowing patients to lead active lives and achieve associated quality of life improvements. However, concizumab is not suitable for on demand use. All breakthrough bleeds would require concomitant treatment with FIX or rFVIIa consistent with the other antibody-based treatment available in Haemophilia A (Hanley, McKernan et al. 2017, Mahlangu, Dolan et al. 2020).Therefore, it is expected that concizumab will largely replace the need for NovoSeven® RT short-term prophylaxis and significantly reduce the on demand use of rFVIIa.

The introduction of concizumab will fulfil a significant unmet need as HMBwI patients currently do not have access to long-term prophylaxis (Royal, Schramm et al. 2002, Hoots and Nugent 2006, Collins, Faradji et al. 2010, Iorio, Marchesini et al. 2011, Manco-Johnson, Soucie et al. 2017, Castaman 2018, Miesbach, Kittler et al. 2020).

Outcomes

(Please copy the below questions and complete for each outcome)

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator): (please select your response)

☒ Health benefits

☐ Health harms

☐ Resources

☐ Value of knowing

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Currently there are no long-term prophylaxis treatments available to HMBwI patients. The introduction of concizumab to the HMBwI patient management algorithm will provide clinicians with a novel, long-term prophylaxis option. Concizumab also relieves the burden of treatment associated with iv administration as concizumab can be self-administered subcutaneously in the patient's home, resulting in a lower treatment burden which may have the potential to also improve treatment adherence and thereby achieve better clinical outcomes for patients with haemophilia (Hampton, Knoebl et al. 2022).

The following key health outcomes will be measured in assessing the clinical claim for concizumab:

Safety Outcomes: Safety and tolerability of concizumab treatment assessed by incidence and severity of adverse events

Primary effectiveness

- Reduction in number of bleeds over time (bleed rate)
- Prevention of bleeds

Secondary endpoints

- Responder status
- Other bleeding related outcomes such as: reduction in number of joint bleeds over time, reduction in number of target joint bleeds over time, reduces individual bleed rate compared to historical bleed rate and number of treated bleeds per month or year etc.
- HRQoL
- Joint health outcomes
- Chronic pain associated with haemophilia
- Number of missed days of work/activity/school

Healthcare resources

- Cost offsets
- Costs of delivering the intervention
- Costs of managing adverse events or breakthrough bleeding
- Cost per Quality Adjusted Life-Year gained

Proposed MBS items

How is the technology/service funded at present? (for example: research funding; State-based funding; self-funded by patients; no funding or payments):

Concizumab is a novel therapy and is not currently used in patient management of HMBwl, therefore, it is not currently funded nor available.

Please provide at least one proposed item with their descriptor and associated costs, for each population/Intervention: (please copy the below questions and complete for each proposed item)

N/A, this MSAC Application is not seeking the generation of a new MBS item number. The application seeks inclusion of concizumab on in the National Products Price List maintained by the National Blood Authority.

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

Prior to treatment with concizumab, patients will need to have a diagnosis of HMBwl. Table 5 outlines the laboratory tests required to diagnose the presence and severity of inhibitor development in patients diagnosed with Haemophilia B.

Table 5 Investigative tests to confirm Haemophilia B with inhibitors diagnosis

Investigative Tests	Relevant Notes
Development of inhibitors • Coagulation factor inhibitors test	Test based on the inability of normal plasma to correct prolonged APTT (or PT). Further testing is required for quantifying inhibitor levels.
Quantification of inhibitor • Bethesda assay	Inhibitors may be low or high-titre; A low-responding inhibitor is defined as an inhibitor level that is persistently below 5 Bethesda units (BU)/ml, whereas a high-responding inhibitor is defined by a level of at least 5 BU/m

Source: (AHCDO 2016)
Abbreviations: APTT, Activated partial thromboplastin time; Bethesda units, BU; PT, Prothrombin time.

These tests are currently performed as part of the regular standardised evaluations recommended by AHCDO if the development of inhibitors is suspected (AHCDO 2016).

REDACTED. No further tests to quantify or diagnose these patients will be required. Note that current prevalence and utilisation data is derived from the 2020-21 and 2021-22 ABDR report (National Blood National Blood Authority 2021 and National Blood Authority 2022). Data from the updated ABDR can be provided to MSAC as part of the ADAR, if available.

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology? (please highlight your response)

Yes **No**

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

There is no change to the clinical management algorithm of HMBwl patients prior to the use of concizumab prophylaxis compared to NovoSeven® RT as on demand or short-term prophylaxis.

At the point of the clinical management algorithm where patients would receive concizumab, patients have already been diagnosed with inhibitors. The development of inhibitors in HMB patients is assessed as part of regular standardised evaluations that all HMB patients receive. Currently, patient monitoring involves regular (at least every 12 months) standardised evaluation of indicators such as bleeds, joint health, venous access, transfusion-transmitted infections, inhibitor development, overall psychosocial status and dental or oral health (AHCDO 2016). This is to ensure a longitudinal assessment for individual patients and aims to identify new or potential problems so that treatment plans can be modified (AHCDO 2016). Therefore, no further testing is required to determine eligibility for concizumab prophylaxis.

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

To optimise the maintenance dose of concizumab, four weeks post initiation of concizumab, measurement of the plasma concentration of concizumab via a specific ELISA is required. Upon identification of a patient's concizumab plasma concentration result, a healthcare professional is to calculate the individual's maintenance dose, assist the patient in rounding off and identifying the

appropriate injectable dose on the pen and train the patient and/or their carer on how to administer concizumab within the first four weeks of commencing concizumab. After initial training by a healthcare professional, concizumab will be either self-administered by the patient or administered by a carer; no further health resource utilisation is required.

It is proposed that the blood collection for the concizumab-ELISA test will be covered under MBS item number #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.

Novo Nordisk will cover all costs associated with the actual concizumab-ELISA assay; the MBS item would cover the remaining laboratory costs ensuring patients are not left with out of pocket expenses.

As experienced in the Novo Nordisk Explorer clinical trial program, breakthrough bleeding may occur in some patients. Treatment of breakthrough bleeds would most likely require concomitant, on demand treatment with NovoSeven® RT. This is consistent with the other antibody-based treatment available in Haemophilia A (Hanley, McKernan et al. 2017, Mahlangu, Dolan et al. 2020).

Explain what other healthcare resources are used in conjunction with the comparator health technology:

Most patients on short-term prophylaxis administer treatment at home. In this setting Novo Nordisk provides the required resources for NovoSeven® RT administration therefore no MBS items or healthcare resources that act as a cost to the Government are involved.

NovoSeven® RT dosing is variable depending on the scenario in which it is required and the individual requirements of the patient. In the instance of a spontaneous or traumatic bleeding episode, a patient is treated with iv NovoSeven® RT every two to three hours until the bleed is controlled (NovoSeven® RT Product Information 2023). In cases of extended bleeds, NovoSeven® RT should be administered in hospitals preferably specialised in treatment of haemophilia patients with coagulation FVIII or IX inhibitors, or if not possible in close collaboration with a physician specialised in haemophilia treatment. If bleeding is not kept under control, hospital care is mandatory. As part of short-term prophylaxis in patients with frequent bleeding episodes, or as surgical prophylaxis, NovoSeven® RT may be administered intravenously once daily for up to three months (NovoSeven® RT Product Information 2023).

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

Patients treated with concizumab require a maintenance dose be calculated to optimise their therapy, this requires a concizumab-ELISA test be completed (which will be funded via MBS item #66812 and Novo Nordisk). Upon identification of a patient's concizumab plasma concentration result, assistance from a health care professional is required to calculate the maintenance dose, identify the appropriate injectable dose on the pen and train the patient and/or their carer on how to administer concizumab. After initial training by a healthcare professional, concizumab will be either self-administered by the patient or administered by a carer; no further health resource utilisation is required.

As noted previously, healthcare resources currently required for treatment with NovoSeven® RT are provided by Novo Nordisk in the NovoSeven® RT kit at no cost to the Government.

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any re

quired tests or healthcare resources, *after* the use of the proposed health technology:

Introduction of concizumab to Australian patients will provide a novel first-line prophylactic, easy-to administer, subcutaneous therapy for HMBwI patients. Patients on concizumab will be required to have blood taken for a concizumab-ELISA test to determine their maintenance dose. It is proposed that the blood collection for the concizumab-ELISA test will be covered under MBS item number #66812. Novo Nordisk intends to cover all remaining costs associated with the actual concizumab-ELISA assay and the MBS item would cover the remaining laboratory costs ensuring patients are not left with out of pocket expenses.

Patients on concizumab will continue to undergo regular standardised evaluation as per the current standard of care.

Additionally, in the event that a patient experiences a breakthrough bleed, the patient would most likely receive concomitant treatment with NovoSeven® RT to treat the bleed (Hanley, McKernan et al. 2017, Mahlangu, Dolan et al. 2020).

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the comparator health technology:

Currently, patient monitoring involves regular (at least every 12 months) standardised evaluation of indicators such as bleeds, joint health, venous access, transfusion-transmitted infections, overall psychosocial status and dental or oral health (AHCDO 2016). This is to ensure a longitudinal assessment for individual patients and aims to identify new or potential problems so that treatment plans can be modified (AHCDO 2016).

A key part of patient assessment is the monitoring of treatment efficacy. If treatment efficacy is considered suboptimal i.e., patients continue to experience HMB related symptoms, then the dosage and frequency of treatment with rFVIIa therapies will be adjusted. There are no methods to monitor the efficacy of rFVIIa. Clinicians are reliant on subjective reports by the patient and few, if any, objective measures (National Hemophilia Foundation 2018).

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:

The concizumab-ELISA is specific to concizumab and therefore is not required for the comparator health technology.

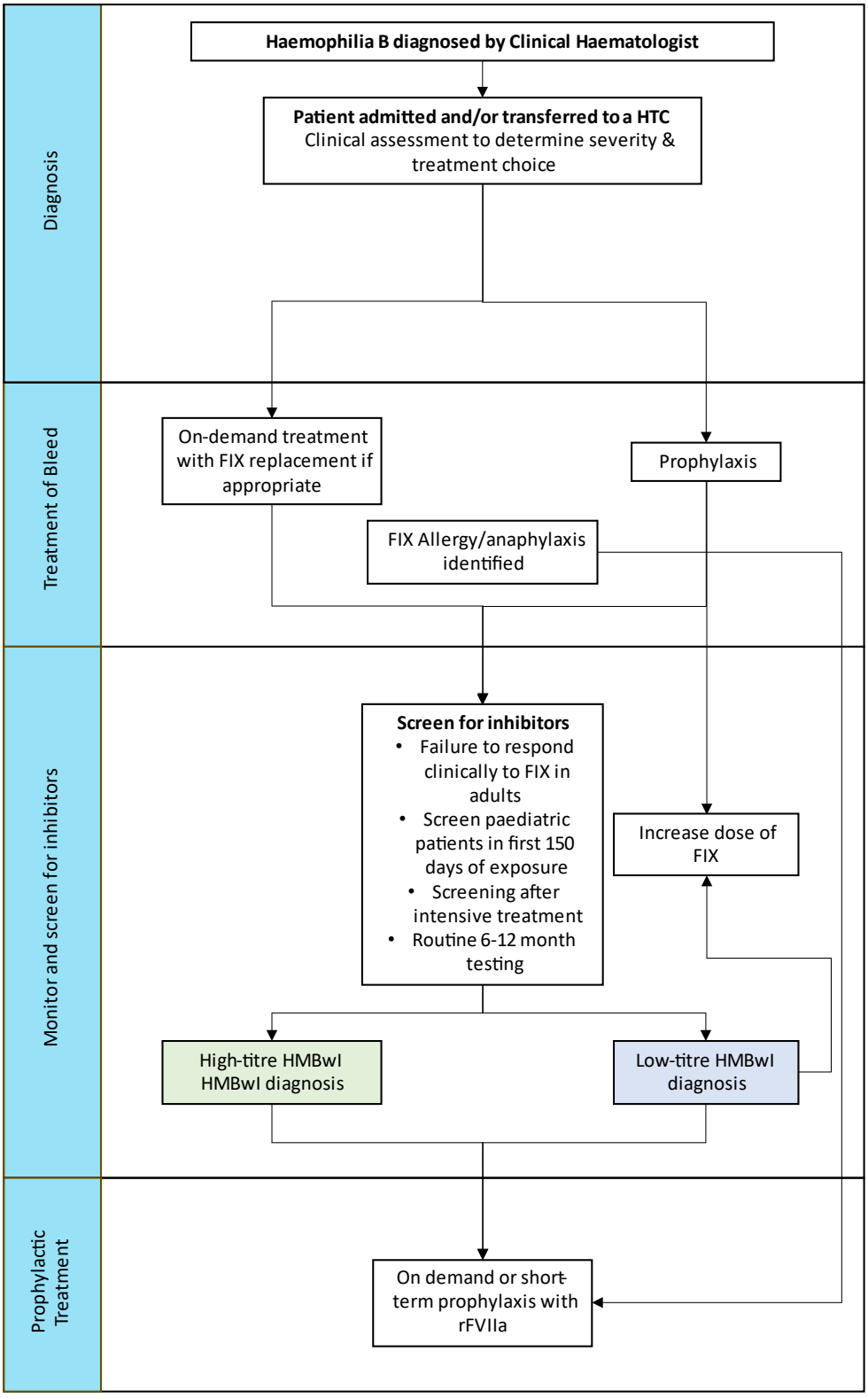
Current monitoring involves regular standardised evaluation. There will be a reduced need to evaluate venous access and adjust treatment regimen due to the subcutaneous administration and early dose optimisation of concizumab respectively. HMBwI patients treated with concizumab will require reduced close monitoring as concizumab exerts its effect via a different method of action compared to current HMBwI standard of care reducing the likelihood of anaphylactic reactions. Monitoring can be incorporated into existing standardised evaluation occurring as part of the comparator's clinical management pathway.

Algorithms

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

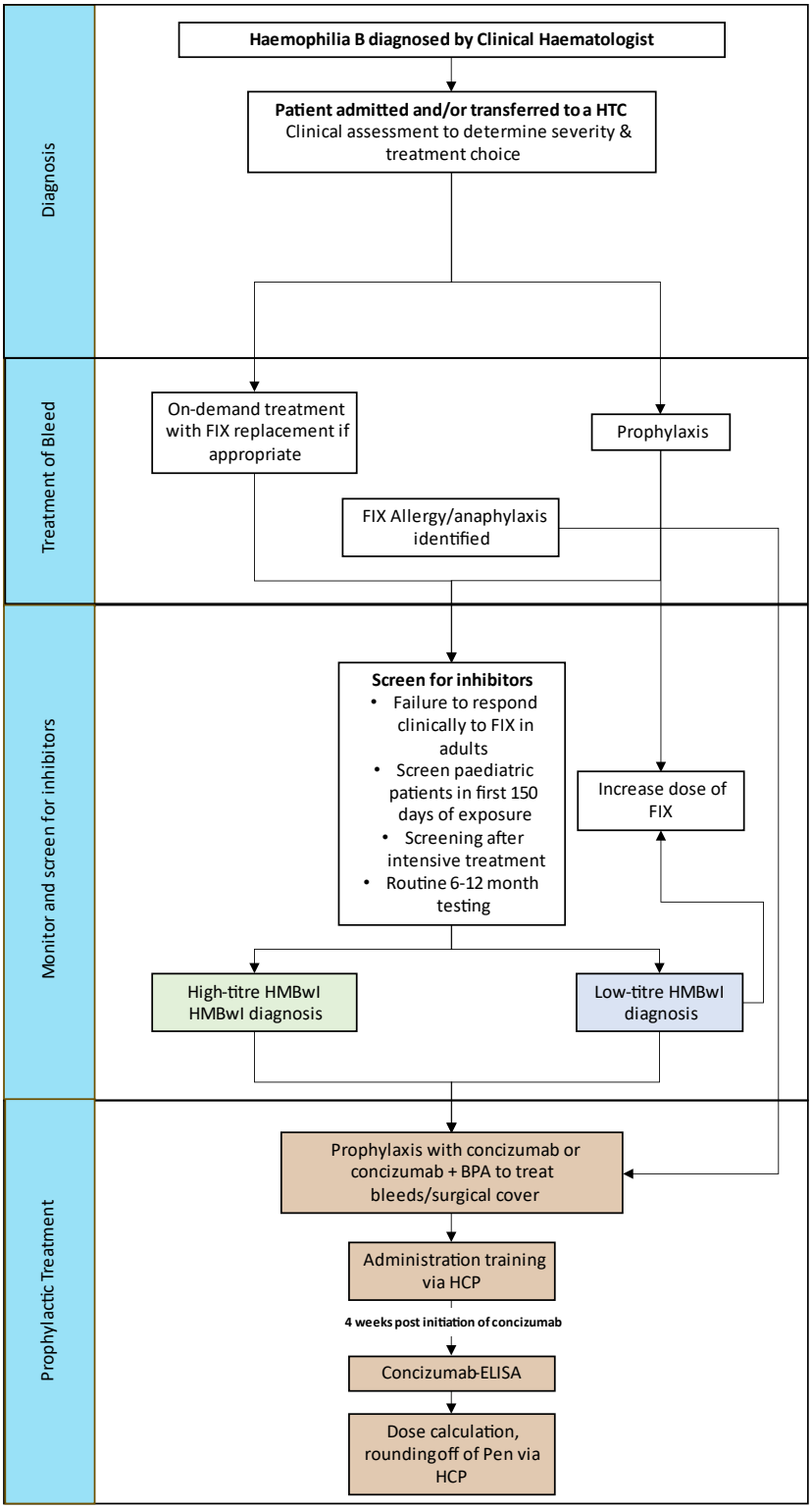
In PDF 'Current_Management_Algorithm_HMBwI' is the current treatment pathway, which is based on that provided in the ratified PICO for emicizumab (MSAC 1510 Ratified PICO) for HMAwI adapted to reflect the pathway for HMBwI.

Figure 3 Current clinical management algorithm for patients with Haemophilia B with inhibitors



Abbreviations: FIX, Factor IX; HMB, Haemophilia B; HMBwI, congenital haemophilia B with inhibitors; HTC, Haemophilia treatment centre; rFVIIa, recombinant activated Factor VII
Depicted in PDF 'Proposed_Management_Algorithm_HMBwI' is the proposed treatment pathway where concizumab presents an alternative to BPAs in the HMBwI population.

Figure 4 Proposed clinical management algorithm for patients with Haemophilia B with inhibitors



Abbreviations: BPA, bypassing agent; FIX, Factor IX; HCP, Healthcare professional; HMBwI, congenital haemophilia B with inhibitors; HMB, Haemophilia B; HTC, Haemophilia treatment centre

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)? (please select your response)

☒ Superior

☐ Non-inferior

☐ Inferior

Please state what the overall claim is, and provide a rationale:

The overall clinical claim is that concizumab is associated with superior health outcomes for HMBwI through improved efficacy (prevention and reduction in bleeds and improved quality of life) and at least non-inferior safety, if not superior safety, in comparison to treatment with NovoSeven® RT administered in either an on demand or short-term prophylactic manner.

The rationale for this claim are the results from the Explorer7 trial. The Explorer7 trial demonstrated that patients in the concizumab arm experienced effective prophylaxis, reduced bleeding, improved quality of life, reduced treatment burden and morbidity and an overall preference for concizumab compared to BPAs (Thornburg and Duncan 2017, Lee, Cepo et al. 2019, Hampton, Knoebl et al. 2022).

The Explorer7 trial (n = 127) was designed to evaluate the efficacy and safety of daily concizumab prophylaxis administered subcutaneously in haemophilia patients with inhibitors. The primary objective of Explorer7 was to compare the effect of concizumab prophylaxis with no prophylaxis in reducing the number of bleeding episodes in adult and adolescent haemophilia patients with inhibitors. Concizumab prophylaxis was superior to no prophylaxis in reducing annualised bleeding rates (ABRs), joint bleeding and target joint bleeding in haemophilia patients with inhibitors. Concizumab was associated with an 86% reduction in ABR vs no prophylaxis (rate ratio 0.14 [95% CI, 0.07 to 0.29]; P<0.001). The median ABR for patients on concizumab prophylaxis was 0.0 vs 9.8 for patients on no prophylaxis and approximately 60% of patients on concizumab prophylaxis had no bleeding episodes. These values align with current benchmarks of effective haemophilia treatment. Treatment with concizumab was generally well tolerated in patients. The most frequently reported treatment-related adverse events across all concizumab treatment arms were general disorders and administration site conditions (17.3%). The rate of serious adverse events was

comparable between concizumab and no prophylaxis arms (0.4 and 0.2 SAEs per patient years exposure, respectively). There was no significant difference in patient-reported outcomes between treatment groups however, 93% of patients preferred concizumab to their previous treatment. Overall, the study showed that in haemophilia patients with inhibitors, concizumab improves ABR, joint bleeding and target joint bleeding. Additionally, concizumab was well tolerated, sustained quality of life and was the preferred treatment for prophylaxis (Matsushita, Shapiro et al. 2023, van den Berg and Srivastava 2023).

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

A requestor would prescribe concizumab over NovoSeven® RT as concizumab is the only available long-term prophylaxis therapy for HMBwI patients. Concizumab can provide improved clinical outcomes, improved patient quality of life and improved treatment adherence compared to on demand or short-term use of BPAs (Lee, Cepo et al. 2019, Hampton, Knoebl et al. 2022, Matsushita, Shapiro et al. 2023).

The need for regular iv administration is a disadvantage of NovoSeven® RT therapy and represents a significant treatment burden and morbidity that may affect patient adherence (Thornburg and Duncan 2017).

Treatment with concizumab fulfils these unmet needs by allowing patients to self-administer via an easy-to-use pen that can be stored at room temperature (after first use). Concizumab can be administered immediately from the prefilled pen device to support fast subcutaneous administration and minimal discomfort. Concizumab has been demonstrated to have a statistically significant lower treatment burden compared to iv injection of replacement factor products, the observed improvements may have the potential to also improve treatment adherence and thereby, achieve better clinical outcomes for patients (Hampton, Knoebl et al. 2022). Furthermore, the combination of effective prophylaxis and reduced bleeding (especially in HMBwI) together with lower treatment burden of subcutaneous delivery resulted in a clear patient preference in favour of concizumab compared to iv injection replacement factor products (Hampton, Knoebl et al. 2022). Concizumab has also demonstrated an improved quality of life in clinically relevant domains such as physical function, vitality, and bodily pain (Lee, Cepo et al. 2019).

Identify how the proposed technology achieves the intended patient outcomes:

There is no long-term prophylaxis treatment available for patients with HMBwI. The need for more effective, less burdensome, long-term prophylaxis treatment options is particularly urgent in haemophilia patients who develop inhibitors (Butterfield, Hege et al. 2020, Mancuso, Mahlangu et al. 2021). The greatest unmet need is in those with HMBwI, who have been clinically the most underserved population (Hermans, Giangrande et al. 2020). The management of patients with inhibitors is currently much more difficult than for noninhibitor patients, since the partial or complete lack of efficacy of factor replacements greatly increases the complexity of preventing and treating bleeds and their deleterious consequences, particularly arthropathy (Castaman and Linari 2018, D'Angiolella, Cortesi et al. 2018, Ragni, Berntorp et al. 2020). High-titre inhibitors pose a particular challenge, with a reliance on BPAs requiring frequent iv infusion (Butterfield, Hege et al. 2020, Ragni, Berntorp et al. 2020). Currently, there are no nonfactor prophylactic treatments available for the treatment of HMBwI, while data on the prophylactic use of BPAs in HMBwI are somewhat limited, and thus questions around the effectiveness of such regimens remain (Dolan, Benson et al. 2018).

The WFH currently has no recommendation on prophylaxis in HMBwI due to a lack of efficacious and safe treatment options (Ragni, Berntorp et al. 2020), despite the widely established benefits of prophylaxis in reducing bleed rates and slowing disease progression (Royal, Schramm et al. 2002, Hoots and Nugent 2006, Collins, Faradji et al. 2010, Iorio, Marchesini et al. 2011, Manco-Johnson, Soucie et al. 2017, Castaman 2018, Miesbach, Kittler et al. 2020).

Concizumab fulfils this unmet need and the intended patient outcomes by:

- Providing HMBwI patients with a novel, first-line prophylaxis therapy, where there is currently none
- Reduced treatment burden and elimination of morbidity associated with iv injection for HMBwI patients who can administer their treatment via the easy-to-administer, prefilled pen that can be stored at room temperature (after first use) allowing for immediate and fast subcutaneous administration with minimal discomfort
- Improved quality of life as demonstrated by the reduction in bleeds, improved joint health and reduced pain, outcomes of the prophylactic once-a-day treatment

For some people, compared with the comparator(s), does the test information result in: (please highlight your response)

A change in clinical management?	**Yes**	No
A change in health outcome?	**Yes**	No
Other benefits?	**Yes**	No

Please provide a rationale, and information on other benefits if relevant:

Patients' quality of life and treatment adherence are two additional benefits that are associated with concizumab prophylaxis. Patients on daily subcutaneous concizumab prophylaxis generally reported better scores on generic (SF-36v2) and disease-specific (Haem-A-QoL) quality of life questionnaires when compared with patients treated on demand (Shapiro, Abraham et al. 2022). The combination of effective prophylaxis and reduced bleeding (especially in HMBwI) together with lower treatment burden of subcutaneous delivery resulted in a clear patient preference in favour of concizumab prophylaxis compared to iv injection replacement factor products (Matsushita, Shapiro et al. 2023).

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1.	A phase 1, multicentre, randomised, double-blind, placebo controlled, single dose, dose-escalation trial. In each dose cohort, trial participants were randomised 3:1 to receive a single dose of concizumab or placebo respectively.	NCT01228669 Inhibition of Tissue Factor Pathway Inhibitor (TFPI) as a Treatment for Haemophilia: Rationale with Focus on Concizumab (Explorer 1)	To investigate the safety, pharmacokinetics (how the trial drug is distributed in the body) and pharmacodynamics (physiological effects of the drug on the body) of concizumab administered intravenously and subcutaneously to healthy male subjects and subjects with haemophilia A or B Safety of NNC 0172-0000-2021 in Healthy Male Subjects and Subjects With Haemophilia A or B	2018 Chowdary P et al. Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial (wiley.com)	June 2018
2.	A phase 1, multicentre, Open Labelled, Multiple Dosing Trial Investigating Concizumab Administered Subcutaneously to Healthy Male Subjects and Haemophilia Subjects	NCT01631942 Concizumab, an anti-tissue factor pathway inhibitor antibody, induces increased thrombin generation in plasma from haemophilia patients and healthy subjects measured by the thrombin generation assay (Explorer 2)	The aim of this trial is to investigate the effects of concizumab on thrombin generation using the thrombin generation assay administered subcutaneously in healthy male subjects and haemophilia subjects.	2017 Waters EK et al	September 2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
3.	A phase 1, multicentre, Randomised, Placebo Controlled, Double Blinded, Multiple Dose, Dose-escalation Trial Investigating Concizumab Administered Subcutaneously to Haemophilia A Subjects (Explorer™3)	NCT02490787 A randomised trial of safety, pharmacokinetics and pharmacodynamics of concizumab in people with haemophilia A	This trial is conducted globally. The aim of this trial is to investigate safety, pharmacokinetics (the exposure of the trial drug in the body) and pharmacodynamics (the effect of the investigated drug on the body) of concizumab administered subcutaneously to haemophilia A subjects.	2018 Eichler H et al.	September 2018
4.	A phase 2, multicentre, Randomised, Open-Label, Controlled Trial Evaluating the Administration of Concizumab in Haemophilia A and B Patients With Inhibitors (Explorer™4)	NCT03196284 Subcutaneous concizumab prophylaxis in hemophilia A and hemophilia A/B with inhibitors: phase 2 trial results Concizumab: a novel anti-TFPI therapeutic for hemophilia	The aim of the trial is to assess the safety and efficacy of concizumab administered subcutaneously once daily in preventing bleeding episodes in haemophilia A and B patients with inhibitors.	2019 Shapiro AD et al. 2021 Shapiro AD et al.	November 2019 January 2021
5.	A phase 2, multicentre, single-arm, open-label Trial Evaluating the Administration of Concizumab in Patients With Severe Haemophilia A Without Inhibitors (Explorer™5)	NCT03196297 Subcutaneous concizumab prophylaxis in hemophilia A and hemophilia A/B with inhibitors: phase 2 trial results Concizumab: a novel anti-TFPI therapeutic for hemophilia	The aim of the trial is to assess the safety and efficacy of concizumab administered subcutaneously once daily in preventing bleeding episodes in patients with severe haemophilia A without inhibitors.	2019 Shapiro AD et al. 2021 Shapiro AD et al.	November 2019 January 2021

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
6.	Prospective, Multinational, Noninterventional Study in Haemophilia A and B Patients With or Without Inhibitors Treated According to Routine Clinical Treatment Practice (Explorer™6)	NCT03741881 Real-World Unmet Needs of Patients with Haemophilia A/B with or without Inhibitors: Historical Haemophilia Characteristics from Patients Entering a Noninterventional Study	This study collects data on bleeds and data related to quality of life in people with severe congenital (a disease existing from birth) haemophilia A and B, with or without inhibitors. The aim for the study is to look at the number of bleeds when on usual treatment for haemophilia.	2022 Windyga et al.	July 2022
7	In this Phase 3 multicentre, randomised study, patients were randomised 1:2 to no prophylaxis (arm 1; ≥24 weeks) or concizumab prophylaxis (arm 2; ≥32 weeks), or assigned to concizumab prophylaxis (arms 3&4). (Explorer™7)	NCT04083781 Concizumab Prophylaxis in Patients with Haemophilia A or B with Inhibitors: Efficacy and Safety Results from the Primary Analysis of the Phase 3 Explorer7 trial	The aim of the trial was to assess the efficacy and safety of concizumab in patients with Haemophilia A and B, with inhibitors	2022 Jimenez Yuste et al. 2023 Matsushita et al.	July 2022 August 2023

* Categorise study design, for example meta-analysis, randomised trials, nonrandomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post recruitment.

*** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).

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