Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1805 – Concizumab for routine prophylaxis to prevent bleeding in patients with haemophilia B

Applicant: **Novo Nordisk Pharmaceuticals Pty. Limited**

Date of MSAC consideration: **1 April 2026**

1. 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 patients with congenital haemophilia B, with or without inhibitors, who require prophylaxis was received from Novo Nordisk Pharmaceuticals Pty Ltd by the Department of Health, Disability and Ageing.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported public funding of concizumab (Alhemo®) for patients ≥12 years of age with congenital haemophilia B (HMB) with inhibitors (HMBwI) who require prophylaxis, but did not support listing for patients with HMB without inhibitors. MSAC noted that concizumab may be listed on the National Blood Authority's (NBA's) National Product Price List (NPPL).

MSAC considered there is a high unmet clinical need for the small number of patients with HMBwI as currently there are no available long-term effective prophylaxis options to prevent bleeds. The available evidence suggests concizumab may have similar efficacy compared with on-demand therapy regarding bleeding rates (because although the evidence showed reducing bleeding rates with concizumab, this was based on combining data across hemophilia A and HMB patients), and an acceptable safety profile. MSAC considered it was difficult to assess the effectiveness of concizumab in HMBwI due to small patient numbers, and limited follow-up. MSAC considered that while the clinical evidence against the comparator of on-demand treatment with bypassing agents (BPAs) was very limited, it was acceptable in the context of a very small patient population with a high unmet need for a treatment to prevent bleeds. MSAC also noted practical and quality of life benefits of concizumab, including ease of administration and improved access which was highlighted in the public consultation feedback. MSAC's support is conditional on a substantial price reduction with a cap on the number of patients per year (with a 100% rebate) to manage the risk of use outside the HMBwI population. MSAC advised the eligible population should be explicitly defined to ensure the funded population with HMBwI was aligned with the clinical trial population which only included patients with moderate-severe and severe disease.

MSAC did not support public funding of concizumab for the HMB population without inhibitors because the evidence did not demonstrate non-inferior effectiveness compared with intravenous Factor IX (FIX) prophylaxis. MSAC considered the comparison of bleeding rates suggested that patients using concizumab could have a higher rate of bleeds than patients using FIX prophylaxis. MSAC advised that a resubmission for this population would require better evidence of

favourable clinical effectiveness including longer duration of comparative evidence for effectiveness and safety outcomes including near-market comparators marstacimab and etranacogene dezaparvovec. MSAC considered there is a clinical need for a subcutaneous treatment option for the HMB population.

MSAC advised the NBA to undertake an evaluation of existing haemophilia products that have not undergone a health technology assessment, to establish cost-effective prices, as the cost-effectiveness of these products has not yet been established.

Consumer summary

This application from Novo Nordisk requested funding for concizumab for patients ≥12 years of age with either congenital haemophilia B without inhibitors or haemophilia B with inhibitors who require preventative treatment (prophylaxis). The application requested funding through the National Blood Authority's (NBA's) National Product Price List (NPPL).

Haemophilia B is a rare genetic bleeding condition in which a person's blood does not clot properly due to low levels of Factor IX (9), a blood clotting protein. This can lead to prolonged bleeding and spontaneous bleeding into joints and muscles, which can cause pain and long-term damage.

Haemophilia B is usually treated by administering infusions of Factor IX replacement therapy into a vein (intravenously). This is given either regularly (prophylaxis) or on-demand (as needed) or as treatment when bleeding occurs. However, a very small number of patients with haemophilia B develop inhibitors. This is where their immune systems produce antibodies that target the replacement Factor IX and stop it from working. Currently, the only treatment option for haemophilia B with inhibitors patients is on-demand intravenous administration of bypassing agent NovoSeven RT. It can only be used for prophylaxis short-term for up to 3 months at a time (e.g. around the time of surgery) or to treat bleeds.

Concizumab is a prophylactic treatment given daily via small injections into the tissue just under the skin (subcutaneous) that can be self-administered. It works differently from factor replacement therapies by activating the production of another blood clotting protein, Factor X (10). Because concizumab acts on Factor X (not Factor IX) and is not a factor replacement therapy, it may be used to treat patients with haemophilia B either with or without inhibitors.

MSAC noted that consumer feedback on concizumab was generally positive, with benefits including easier administration than intravenous treatments, improved equity of access for people in rural and remote locations, and more treatment options for people with haemophilia. MSAC noted the Haemophilia Foundation Australia input, as it provided valuable feedback about the issues that patients with haemophilia face, particularly patients with inhibitors who do not have as effective and manageable treatments, and feedback regarding experiences with concizumab treatment.

For patients with haemophilia B with inhibitors, MSAC noted the results of the studies did show that patients appeared to have fewer bleeding episodes when they used concizumab compared with on-demand treatment with bypassing agents. However, the statistical analysis showed results favouring concizumab compared to on-demand treatment with bypassing agents could be due to chance. This was because the available studies included very small number of patients with haemophilia B who had inhibitors. Also, some of the evidence combined results from patients with either haemophilia A with inhibitors or haemophilia B with inhibitors. This made it difficult to determine the true effect in the haemophilia B with inhibitors population. MSAC considered that concizumab is effective for preventing bleeding; however, there is insufficient evidence to show that concizumab is more effective than current on-demand treatment with bypassing agents.

MSAC considered concizumab was acceptably safe compared to on-demand treatment with bypassing agents. MSAC did note that patients with haemophilia B with inhibitors currently do not have access to long-term prophylactic treatment and have a high unmet clinical need.

Consumer summary
MSAC acknowledged that due to the rarity of haemophilia B, especially haemophilia B with inhibitors, it may not be possible to generate stronger evidence in the foreseeable future. For patients with haemophilia B without inhibitors, MSAC considered that the evidence did not show concizumab was effective as existing Factor IX prophylactic treatment. The studies reported a higher rate of bleeding with concizumab compared with factor IX prophylactic treatment. Some patients had more bleeds after switching to concizumab from Factor IX prophylaxis. MSAC considered most patients in Australia use extended half-life Factor IX treatment and this could be more effective than the standard half-life Factor IX treatment used in the studies. MSAC supported public funding of concizumab for patients with haemophilia B with inhibitors. The clinical evidence was considered acceptable given the very small patient population and their high clinical need for an effective treatment to prevent bleeding. MSAC advised that its support was based on a price reduction for concizumab. This is because of the clinical evidence could not show that concizumab was better than current treatments for patients with haemophilia B with inhibitors. MSAC advised that the number of treated patients per year is capped at the number of patients with haemophilia B with inhibitors, with the company to pay the full cost of treatment for any additional patients. **MSAC's advice to the Commonwealth Minister for Health, Disability and Ageing** MSAC supported public funding of concizumab for patients ≥12 years of age with congenital haemophilia B with inhibitors who require prophylaxis. MSAC considered that concizumab was shown to reduce bleeding relative to on-demand treatment with BPAs although this was based on evidence that combined the results of haemophilia A and haemophilia B patients. MSAC also considered that concizumab reduced treatment burden in the small haemophilia B with inhibitors population who currently do not have access to a regular preventative treatment option and have a high unmet clinical need. MSAC did not support listing of concizumab for patients ≥12 years of age with haemophilia B without inhibitors as it considered that the available evidence showed that concizumab was not as effective as current treatments and some patients may have more bleeds with concizumab.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from Novo Nordisk requested listing of concizumab (Alhemo®) on the National Blood Authority's (NBA's) National Product Price List (NPPL) for patients ≥12 years of age with congenital haemophilia B (HMB), with (HMBwI) or without inhibitors, who require prophylaxis.

Concizumab is a monoclonal antibody that targets tissue factor pathway inhibitor (TFPI), a regulator of the coagulation process. By binding to TFPI, concizumab enhances coagulation through directly preventing Factor Xa (FXa) inhibition and indirectly preventing activated Factor VII (FVIIa) inhibition. As concizumab's mechanism of action is independent of Factor IX (FIX) and Factor FVIII (FVIII), its effectiveness is not affected by the presence of inhibitors to these factors.

MSAC also noted the position of the pre-MSAC response that the comparator for the HMBwI population should be both on-demand therapy with bypassing agents (BPAs) and short-term prophylaxis. However, MSAC agreed with ESC that the appropriate comparator for this population was on-demand therapy with BPAs.

MSAC noted that consultation feedback, including from patients who had received concizumab in clinical trials and from Haemophilia Foundation Australia (HFA), was supportive of listing for the HMBwI population. MSAC noted that the feedback highlighted benefits to patient convenience,

including ease of administration via subcutaneous injection (especially for those with reduced manual dexterity) allowing for self-administration and better self-management, and reduced treatment burden compared with travelling to and attending treatment centres for intravenous therapies. MSAC also noted the feedback on reported improvements in quality of life (QoL) and independence. In addition, consultation feedback identified potential equity benefits, particularly improved access for patients in regional and remote areas and a broader range of treatment options for haemophilia patients.

The applicant was granted a hearing. At the hearing, representatives of the applicant emphasised the rarity of HMBwI, noting that the eligible population in Australia is small (fewer than redacted patients). The applicant's clinical expert advised that it was highly unlikely the estimated number of patients will increase substantially in the foreseeable future. The hearing highlighted the significant unmet clinical need for patients with HMBwI, given the lack of effective prophylaxis. Representatives also noted that concizumab, as a subcutaneous therapy, may reduce treatment burden and improve QoL, with patient preference driven by ease of administration.

MSAC noted the evidence base supporting the application comprised the Explorer trial series (Explorer6, -7 and -8). For the HMBwI population, the clinical evidence for the effectiveness of concizumab was informed by Explorer6 and Explorer7 studies. These studies included both HMB and Haemophilia A (HMA) populations. MSAC noted the lack of information on the types of prophylaxis (standard half-life [SHL] or extended half-life [EHL]) and frequency of prophylaxis used in the trials, and that it was unclear whether the trial practice reflected Australian standards of care. MSAC also noted concerns that some additional or potential comparators (such as emerging non-factor therapies) were not included, and that the comparator selection did not adequately align with the PICO. Therefore, MSAC considered that this limited the applicability of the evidence base to the Australian setting.

MSAC considered the safety evidence was limited and non-comparative. MSAC considered non-inferior safety compared with SOC was not established. The Explorer7 & 8 trials, encompassing both patients with HMA and HMB (both with and without inhibitors), reported a thrombosis risk with concizumab (non-fatal thromboembolic events), which led to temporary trial suspension and subsequent protocol modifications (including dose titration and monitoring), after which no further events were reported. MSAC also noted hypersensitivity and injection site reactions leading to treatment discontinuation in a small proportion of patients. MSAC considered that the safety profile appeared to be acceptable in the context of a severe and moderately severe haemophilia population.

For the patients with HMBwI, MSAC noted that annualised bleed rate (ABR) was lower with concizumab than with on-demand treatment (2.2 vs 7.2), but that this reduction was not statistically significant. MSAC noted that a statistically significant reduction in the ABR was only observed when HMA and HMB populations were combined and was driven primarily by the HMAwI subgroup. MSAC therefore considered the evidence did not support the claim of superior comparative effectiveness in HMBwI, although point estimates suggested improved bleeding control compared with no prophylaxis. MSAC noted that QoL data favoured concizumab but were subjected to potential bias due to small sample size, selective reporting with substantial missing data and open-label of the trial design. However, MSAC noted that consumer feedback provided supportive evidence of improved daily functioning, reduced treatment burden and increased convenience. MSAC acknowledged that, given the rarity of the HMBwI condition, more robust evidence is unlikely to be generated in the foreseeable future. MSAC considered that the clinical claim of superior efficacy for HMBwI patients was not established and instead considered that concizumab may have similar efficacy compared with on-demand therapy using BPAs. MSAC considered the clinical evidence for HMBwI was acceptable in the context of a very small patient population with a high clinical need for a treatment to prevent bleeds.

For patients with HMB without inhibitors, MSAC considered that the clinical evidence did not support the claim of non-inferior effectiveness compared with FIX prophylaxis. MSAC noted that the comparisons were based on historical within-patient data (Explorer6 vs Explorer8), and that mean ABR was higher for concizumab (5.2 vs 3.1) with the upper bound of the confidence interval of the ABR ratio exceeding the pre-specified non-inferiority margin. MSAC considered the analysis excluding an outlier (one patient with a large increase in bleeds on concizumab) was not appropriate, as such variability would be expected in clinical practice and would have an impact on measured effectiveness. MSAC also noted significant variability in bleeding outcomes, with some patients experiencing increased bleeding following transition to concizumab from FIX prophylaxis. MSAC further considered that current Australian standard of care (SoC), including EHL prophylaxis, may be more effective than the prophylaxis used in the Explorer trial series, suggesting that concizumab may be less effective than existing treatments for Australian patients with HMB.

MSAC agreed with ESC on the requested re-specified (see Table 29) economic evaluations undertaken by the Department. These included that base case economic evaluations presented to MSAC for both populations should adopt a health system perspective and include all relevant costs, regardless of the payer. Thus, MSAC did not accept the applicant's argument that breakthrough bleeding costs should be excluded from the economic evaluation for the with-inhibitors population based on the applicant's proposal to cover these costs.

MSAC noted that the economic model results for both populations were highly sensitive to assumptions regarding comparator costs, treatment compliance, body weight, and administration costs. MSAC considered that the base case in the ADAR likely overestimated comparator costs, in both populations (although the reasons for these overestimates were specific to each population) and that re-specified analyses substantially reduced the estimated cost of concizumab that should be funded.

MSAC noted that the ADAR's cost minimisation analysis for HMBwI estimated the current annual cost of treating a patient with rFVIIa was $**redacted**. This was largely due to the assumption that the comparator was being used as short-term prophylaxis as well as for on-demand treatment. MSAC considered the revised cost-minimisation analysis for HMBwI (Table 29) was more robust as it assumed all patients used what was considered the more appropriate comparator of on-demand rFVIIa treatment, appropriately accounted for the cost of rFVIIa for the treatment of breakthrough bleeds that occur on concizumab, and used the dose and ABR rates for patients using on-demand rFVIIa treatment from the Explorer7 study. This reduced the annual cost of treating HMBwI to $**redacted** (Table 18). This resulted in a price reduction of 87% to achieve a cost-minimised price for concizumab (based on reducing the indication specific unit pricing of concizumab for HMBwI from $**redacted**).

MSAC noted the lack of established cost-effectiveness for currently funded comparator therapies, including BPAs and factor prophylaxis. MSAC noted that this issue has been previously noted in MSAC application 1510.1 (see the public summary document, p. 4) and continues to limit the assessment of cost-effectiveness of new haemophilia treatments. MSAC further noted the requirement to establish the cost-effectiveness of a comparator is clearly stated in the MSAC Guidelines 2021 (TG 2.3), and was included in the PICO Confirmation (pp. 15 and 16) for the current application. MSAC noted that BPAs are high-cost therapies that were funded without formal cost-effectiveness evaluation and as per advice from PASC, may not therefore represent an appropriate basis for cost-minimisation.

MSAC noted that the pre-MSAC response disagreed with many of the economic and financial issues raised by ESC. However, MSAC considered the weak evidence base and lack of

established cost-effectiveness for the comparators made the results of the economic and financial analyses uncertain.

MSAC noted that, for both HMB populations (with and without inhibitors) over 6 years, the estimated base case net cost to the NBA was $redacted. While the estimated net impact to Government health budgets was $0 (cost-neutral), this was based upon the over-optimistic assumptions in the economic evaluation to achieve cost neutrality and that concizumab uptake would merely substitute for the replaced comparator products. However, MSAC noted that the re-specified base case requested by ESC (as per Table 30) which included the re-estimated lower cost neutral prices for concizumab but also revised uptake rates and substitution patterns (due to strong patient preference for subcutaneous administration) decreased the net cost to the NBA but caused the net impact to Government health budgets to no longer be cost-neutral.

Overall, MSAC only supported listing of concizumab for patients ≥12 years of age with congenital HMBwI, who require prophylaxis. MSAC acknowledged this patient population had a significant unmet clinical need without an effective prophylactic treatment option. MSAC did not support the listing of concizumab for HMB without inhibitors due to the lack of evidence to support that claim that concizumab is non-inferior compared with current FIX prophylaxis. MSAC advised that a resubmission for this population would require better evidence of favourable clinical effectiveness including longer duration of comparative evidence for effectiveness and safety outcomes. MSAC also noted that considerations for concizumab in patients with haemophilia B without inhibitors should include comparisons with marstacimab and etranacogene dezaparvovec, which are alternative treatments for this population. However, these other treatments are not yet available public funded treatments but have been considered by MSAC (see MSAC applications 1806 and 1728.1).

MSAC advised that their support for listing of concizumab for HMBwI is based on the unit price of concizumab being reduced to $redacted per unit. MSAC advised that there should be a risk-sharing arrangement based on the highest estimated number of the Australian population of patients with HMBwI, as reported by the applicant (redacted-patients per year). MSAC advised that there should be 100% rebate for use beyond this to manage the risk of use outside the HMBwI population. MSAC noted that if funding was implemented as supported, a post-funding review would be useful to determine and verify the utilisation estimates. MSAC also noted the position of the applicant's pre-MSAC response that the requested population aligned with the ratified PICO and that the term "requires prophylaxis" adequately constrained eligibility for concizumab. However, MSAC considered that further clarification and tightening of wording would be required to ensure the funded population was aligned with the clinical trial population which only included patients with moderate-severe and severe disease.

MSAC advised the National Blood Authority (NBA) to undertake an evaluation of existing haemophilia products that have not undergone a health technology assessment to determine the cost-effectiveness of these products and help determine their cost-effective prices. MSAC advised that a framework for the assessment of haemophilia treatments would be informative to ensure a consistent approach to evaluating current and future therapies. MSAC advised that it would be beneficial if this evaluation and the framework were completed before MSAC considers any further haemophilia treatment products for public funding.

4. Background

MSAC has not previously considered concizumab for the prophylactic treatment of patients with haemophilia B (HMB) or haemophilia B with inhibitors (HMBwI).

MSAC has previously supported the monoclonal antibody therapy emicizumab for haemophilia A (HMA) and haemophilia A with inhibitors (HMAwI) and is currently assessing marstacimab for HMA and HMB without inhibitors. MSAC has also supported a gene therapy for HMB (Table 1).

Table 1 Summary of haemophilia-related applications to MSAC

Application	MSAC Meeting Date	Outcome
Antibody therapies		
1806 – Marstacimab for routine prophylaxis to prevent bleeding in patients with haemophilia	1-2 April 2026	N/A
1510.1 – Emicizumab for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with Haemophilia A	1 - 2 August 2019	Supported
1579 – Emicizumab for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with moderate to severe Haemophilia A (congenital Factor VIII deficiency) WITHOUT Factor VIII inhibitors	1 - 2 August 2019	Supported
1510 – Emicizumab for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with Haemophilia A (congenital Factor VIII deficiency) with Factor VIII inhibitors	22 - 23 November 2018	Not Supported
Gene therapies		
1728.1 – Etranacogene dezaparvovec for the treatment of Haemophilia B	31 July - 1 August 2025	Supported
1728 – Etranacogene dezaparvovec for the treatment of Haemophilia B	1–2 August 2024	Not Supported
1751 – Valoctocogene roxaparvovec gene therapy for congenital haemophilia A	PASC meeting 18-19 April 2024	Withdrawn

MSAC = Medical Services Advisory Committee; NA = not applicable; PASC = PICO Advisory Subcommittee.

5. Prerequisites to implementation of any funding advice

There are currently 4 Australian Register of Therapeutic Goods (ARTG) listings related to this application; 394068, 394065, 394067 and 394066, corresponding to 15 mg/1.5 mL, 60 mg/1.5 mL, 150 mg/1.5 mL and 300 mg/3 mL solutions, respectively, for the concizumab injection prefilled pen.

6. Proposal for public funding

Concizumab is a prescription medicine and potentially a blood-related product that has orphan drug status assigned by the TGA. The application is therefore seeking public funding through listing on the NBA's NPPL. No Medicare Benefits Schedule (MBS) item is required.

An enzyme-linked immunosorbent assay (ELISA) is required for dose setting of concizumab (once only). The costs associated with the concizumab-specific ELISA, including the costs of collecting the sample and sending it to the centralised laboratory for testing, are proposed to be covered by

Novo Nordisk. The Haemophilia Treatment Centre (HTC) will pay for the blood draw and the onsite processing of the sample (centrifugation, freezing, etc.). No MBS item is required.

7. Population

The proposed population is adolescent and adult patients (≥12 years) with congenital HMB (cHMB) where prophylaxis is required to prevent or reduce the frequency of bleeding. This definition aligns with the TGA-registered indication. Patients with and without inhibitors are considered separately.

Haemophilia B with inhibitors

The PICO Set in the ratified PICO confirmation was for patients with HMB with inhibitors.

The development of inhibitors to exogenous Factor IX (FIX) 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. It occurs almost exclusively in patients with severe HMB.

Two bypassing agents (BPAs) are available to treat bleeds; activated prothrombin complex concentrate (aPCC) and recombinant activated human Factor VIIa (rFVIIa). Due to the presence of FIX in aPCC, which may trigger anaphylaxis, rFVIIa is the preferred option. 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. There is no long-term prophylactic treatment available for these patients.

Concizumab is proposed to provide a long-term prophylactic treatment option where none currently exists for HMBwI. Concizumab would replace short-term prophylaxis with rFVIIa but would not replace its use to manage breakthrough bleeds (i.e. on-demand use).

Haemophilia B without inhibitors

The application included a second population, patients with HMB without inhibitors, at the request of the PICO Advisory Subcommittee (PASC).

Intravenous FIX replacement therapy is current standard of care for these patients with HMB requiring prophylaxis. Management using extended half-life products requires intravenous (IV) infusions every 7–14 days imposing a substantial burden on patients and their caregivers. In Australia, the use of the short-acting plasma-derived FIX product MonoFIX VF has been superseded by the use of recombinant SHL and EHL products.

Concizumab is administered subcutaneously and, following training, patients can self-inject. Therefore, concizumab is proposed to provide an alternative prophylactic treatment replacing IV infusion every 1–2 weeks with a daily subcutaneous injection. FIX replacement would still be used to manage breakthrough bleeds.

Some patients may elect to commence prophylactic treatment if a subcutaneous treatment is available. In this case, concizumab would be an addition to the current therapy choice and expand the number of patients with HMB treated prophylactically. The Applicant Developed Assessment Report (ADAR) stated that concizumab is intended for patients with moderate or severe HMB, to align with the clinical trial evidence. However, the TGA-approved indication does not specify disease severity; it only specifies use for patients requiring prophylaxis. Individuals with mild severity would not typically require long-term prophylaxis and typically have low use of IV therapy for bleeding events.

8. Comparator

Haemophilia B with inhibitors

The proposed comparator in the PICO confirmation 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 ADAR has presented the clinical evidence against two separate comparators:

- main comparator: short-term prophylaxis with BPAs
- secondary comparator: on-demand treatment with BPAs (no prophylaxis).

Given that BPAs are only indicated for short-term prophylaxis and concizumab is indicated for long-term prophylaxis, the commentary considered the ADAR's secondary comparator to be the most applicable.

The comparators are reimbursed on the NBA's NPPL.

Haemophilia B without inhibitors

The proposed comparator in the ADAR is standard of care, with clinical evidence presented against 2 separate comparators:

- main comparator: prophylaxis with FIX replacement therapy
- secondary comparator: on-demand FIX replacement therapy following a bleeding episode.

As the indication is patients who require prophylaxis, the commentary considered the ADAR's main comparator to be the most applicable and the secondary comparator to have limited applicability to the proposed indication. However, it is acknowledged that funding of concizumab could expand the indication such that patients not currently on prophylactic therapy elect to commence prophylaxis.

The comparators are reimbursed on the NBA's NPPL under the National Blood Agreement.

Two additional near-market comparators are relevant:

- Etranacogene dezaparvovec, Hemgenix® (MSAC application 1728.1) was supported by MSAC in July 2025 for adults with cHMB without inhibitors. As a gene therapy, Hemgenix® is a one-time treatment designed to eliminate the need for ongoing prophylactic therapy.
- Marstacimab (MSAC application 1806) will be considered by MSAC at the same meeting as concizumab. The application is for HMA and HMB without inhibitors. Like concizumab, marstacimab is a monoclonal, anti-tissue factor pathway inhibitor (TFPI) antibody indicated for routine prophylaxis in severe HMA and HMB. It is injected subcutaneously on a weekly basis.

9. Summary of public consultation input

Consultation input was welcomed from:

1805 – Concizumab for routine prophylaxis to prevent bleeding in patients with haemophilia B	No. of Inputs Received
Organisations (5)	
I am providing input on behalf of a consumer group or organisation. Consumer organisations are not-for-profit organisations representing the interests of healthcare consumers, their families and carers.	2
I am providing input on behalf of a medical, health, or other (non-consumer) organisation. For example, input on behalf of a group of clinicians, research organisation, professional college, or from an organisation that produces a similar service or technology.	3
Grand Total	5

MSAC received consultation input from the following organisations:

- Public Pathology Australia (PPA)
- Australian Haemophilia Centre Directors' Organisation (AHCDO)
- Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ)
- Haemophilia Foundation of Australia (HFA) (2 inputs)

Level of support for public funding

Consultation input was supportive of public funding for concizumab for routine prophylaxis to prevent bleeding in patients with congenital Haemophilia B (cHMB). The HFA stated that the therapy would provide significant benefits to patients.

Comments on PICO

The consultation input agreed with the proposed population. The input noted that people with cHMB and FIX inhibitors are a very rare group and that these patients have one of the greatest unmet needs in the haemophilia population as there is no effective prophylaxis (which is best practice and standard of care). AHCDO described the current treatment burden experienced by this group as high, noting the significant economic costs associated with it and decreased quality of life. HFA was supportive of the recommendation in the PICO confirmation that the population be expanded to include people with haemophilia B without inhibitors.

The consultation input agreed with the proposed comparators, noting that the current standard of care is the use of bypassing agents.

AHCDO noted that the outcome measures listed in the PICO are the outcomes which are part of standard of care and are consistent with those reported in the clinical trials for concizumab.

Perceived Advantages

The consultation input reported a range of perceived benefits of public funding of the proposed intervention. These included: provision of a prophylactic option for treatment, which is the preferred standard of care; 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 and much less painful.
- once opened, consumers can store concizumab at room temperature, which allows users to integrate its use more easily into their daily routines. This may in turn support treatment adherence.
- the mode of administration does not require hand dexterity, so it is easy for people with arthritis or shaky hands to administer.
- the fixed dose prefilled pen means that there are no dose mistakes.
- At a broader level, HFA stated that this provides the potential for the person to increase their participation in personal and family life, the workforce, social activities, travel and physical and recreational activities. It provided case studies from two individuals with experience of concizumab, both of whom described it as life changing.
- AHCDO noted that the proposed eligibility criteria will improve health equity in the haemophilia population as patients with haemophilia B with inhibitors will have access to subcutaneous treatment.

Perceived Disadvantages

There were no disadvantages of public funding identified in the consultation input. However, HFA noted that those on the medication may need additional support/guidance on how to recognise a bleed, how to apply for jobs etc.

Support for Implementation and Issues

Consultation input was supportive of the proposed approach to implementation. AHCDO noted that haemophilia treatment centres (HTC) that have patients who meet the criteria but have not had experience with concizumab will need some education, but that this can be done very quickly as the technology used to administer the medication is easy to use. In addition, HTC clinicians will be familiar with concizumab as data has been presented at numerous local and international meetings.

Public Pathology Australia stated that it does not believe there is any laboratory in Australia that is able to conduct the trough plasma concizumab concentration assay required 4 weeks after drug initiation to help guide maintenance therapy dosing. However, it notes that hospitals who were involved with the concizumab clinical trials will likely have some experience with the drug effect on routine pathology testing. PPA noted that if laboratory monitoring of concizumab is required, new assays may need to be set up.

AHCDO noted that there are good and effective measurements of outcomes through the Australian Bleeding Disorders Registry (ABDR) where patients can record number of bleeds in myABDR. The usage of bypass agents (recombinant FVIIa (NovoSeven) and FEIBA) can also be monitored.

10. Characteristics of the evidence base

Haemophilia B with inhibitors

The evidence base consisted of 2 linked studies: Explorer6 and Explorer7 (Table 2). The pivotal study is Explorer7.

Table 2 Key features of the included evidence for concizumab in HMBwI

Trial/ Study N	Study design Risk of bias	Population	Intervention	Comparator	Key outcomes	Result used in economic analysis
Explorer6[1] NCT03741881 231 (31 HMBwI)	MC prospective cohort (non-interventional) Moderate	Males ≥12 years of age with severe HMA, severe/ moderate HMB or HMAwI or HMBwI of any severity	Treatment according to local standard of care (on-demand or prophylaxis)	N/A	ABR SF-36v2	Yes
Explorer7[2] NCT04083781 52 randomised: Intervention, 33 (HMBwI = 15) Comparator, 19 (HMBwI = 10) 81 allocated to concizumab	MC OL RCT Some concerns	Males ≥12 years of age with HMAwI or HMBwI (any severity) and treated with BPAs in the 24 weeks before screening	Prophylactic treatment with concizumab	On-demand treatment with BPA	ABR AEs SF-36v2 Haem-A-QoL	Yes

ABR = annualised bleeding rate; AE = adverse event; BPA = bypassing agent; Haem-A-QoL = Haemophilia Quality of Life Questionnaire for adults; HMA = haemophilia A; HMAwI = haemophilia A with inhibitors; HMB = haemophilia B; HMBwI = haemophilia B with inhibitors; MC = multicentre; N = number of participants; N/A = not applicable; OL = open label; RCT = randomised controlled trial; SF-36v2 = 36-item Short-Form Health Survey, version 2.
Source: adapted from Table 12 of MSAC 1805 ADAR + in-line commentary.

[1] Windyga J, Apte S, Frei-Jones M, Fujii T, Lyu CJ, Villarreal Martinez L, Sathar J, Stasyshyn O, Tran H, Zozulya N, Brown Frandsen R, Neergaard JS, Thaung Zaw JJ and Mahlangu J (2024) 'Disease and treatment burden of patients with haemophilia entering the explorer6 non-interventional study', *European Journal of Haematology*, 113(5):631–640, doi:10.1111/ejh.14277.

Wheeler AP, Abraham A, Barnes C, Brown Frandsen R, d'Oiron R, Eichler H, Hampton K, López-Jaime FJ, Lyu CJ, Tavares CMM, Nogami K, Sutton C, Windyga J, Zulfikar B and Castaman G (2025) 'Real-World Unmet Needs of Patients With Haemophilia A and Haemophilia B With or Without Inhibitors: End-of-Study Results From the explorer6 Non-Interventional Study', *Haemophilia: The Official Journal of the World Federation of Hemophilia*, 31(5):903–911, doi:10.1111/hae.70051.

[2] Matsushita T, Shapiro A, Abraham A, Angchaisuksiri P, Castaman G, Cepo K, d'Oiron R, Frei-Jones M, Goh A-S, Haaning J, Hald Jacobsen S, Mahlangu J, Mathias M, Nogami K, Skovgaard Rasmussen J, Stasyshyn O, Tran H, Vilchevska K, Villarreal Martinez L, Windyga J, You CW, Zozulya N, Zulfikar B and Jiménez-Yuste V (2023) 'Phase 3 Trial of Concizumab in Hemophilia with Inhibitors', *New England Journal of Medicine*, 389(9):783–794, doi:10.1056/NEJMoa2216455.

Tran H, von Mackensen S, Abraham A, Castaman G, Hampton K, Knoebl P, Linari S, Odgaard-Jensen J, Neergaard JS, Stasyshyn O, Thaung Zaw JJ, Zulfikar B and Shapiro A (2024) 'Concizumab prophylaxis in persons with hemophilia A or B with inhibitors: patient-reported outcome results from the phase 3 explorer7 study', *Research and Practice in Thrombosis and Haemostasis*, 8(4):102476, doi:10.1016/j.rpth.2024.102476.

Explorer7 compared prophylactic treatment with concizumab against on-demand treatment with BPAs in patients with HMAwI and HMBwI. The trial was an open-label RCT conducted across 27 countries (74 sites) that randomised 52 participants (1:2 ratio of control to intervention). The study also included 81 non-randomised participants (including 21 transferred from the Explorer4 trial) who received concizumab prophylaxis. The open-label design of the trial introduces a risk of bias, particularly for patient-reported quality-of-life outcomes, which was compounded by a higher loss to follow-up.

Due to the small number of randomised participants, the ADAR reported data for the combined HMAwI and HMBwI populations, stating that the mechanism of action is the same and therefore the data are applicable.

Explorer6 was an observational prospective cohort study that included a large population of patients with HMBwI. Patients who completed the Explorer6 study were eligible for randomisation into Explorer7. The ADAR used data from Explorer6 to conduct a post-hoc intra-patient analysis comparing concizumab prophylaxis (Explorer7 data) with short-term BPA prophylaxis (Explorer6 data). Seven HMBwI patients were included in the analysis with a 3-week washout period between the two trials.

Safety outcomes were presented from the Explorer7 trial and included all patients with HMBwI who received concizumab (Table 3).

Table 3 Summary of evidence base in the HMBwI population for concizumab prophylaxis (with on-demand BPAs) by comparator

Item	Primary comparison in ADAR[a] – effectiveness	Secondary comparison in ADAR – effectiveness	Safety
Comparator	BPA prophylaxis	On-demand BPAs	On-demand BPAs/ BPA prophylaxis
Evidence base	Interrupted time-series of patients enrolled in Explorer6 (BPA prophylaxis) followed by Explorer7 (concizumab)	Open-label RCT (Explorer7) – Arm 1 (on-demand BPAs) and Arm 2 (concizumab)	Open-label RCT including non-randomised arms and patients who crossed over from Arm 1 (Explorer7) – no comparator
Participants in analysis (n)	7 (all HMBwI)	52 (25 HMBwI)	127 (HMAwI / HMBwI)

BPA = bypassing agent; HMAwI = haemophilia A with inhibitors; HMBwI = haemophilia B with inhibitors; NR = not reported; RCT = randomised controlled trial.
a. BPA prophylaxis was designated the primary comparator by the ADAR but not considered the primary comparator by the commentary.
Source: adapted from Table 13 and narrative (p.56) of MSAC 1805 ADAR + in-line commentary.

Haemophilia B without inhibitors

The evidence base consisted of 2 linked studies: Explorer6 and Explorer8 (Table 4). The pivotal study is Explorer8.

Table 4 Key features of the included evidence for concizumab in HMB without inhibitors

Trial/ Study N	Study design Risk of bias	Population	Intervention	Comparator	Key outcomes	Result used in economic analysis
Explorer6[3] NCT03741881 231 (72 HMB without inhibitors)	MC prospective cohort (non-interventional) Moderate	Males ≥12 years of age with severe HMA, severe/ moderate HMB, or HMAwI or HMBwI of any severity	Treatment according to local standard of care (on-demand or prophylaxis)	N/A	ABR SF-36v2	Yes
Explorer8[4] NCT04082429 63 randomised: Intervention, 42 (HMB = 24) Comparator, 21 (HMB = 12) 85 (30 HMB) allocated to concizumab PPX	MC OL RCT Some concerns	Males ≥12 years of age with severe HMA or severe/ moderate HMB without inhibitors and, unless transferring from Explorer5, with documented clotting factor treatment in the 24 weeks before screening	Prophylactic treatment with concizumab	No prophylaxis, on-demand treatment with clotting factor	ABR AEs SF-36v2 Haem-A-QoL	Yes

ABR = annualised bleeding rate; AE = adverse event; BPA = bypassing agent; Haem-A-QoL = Haemophilia Quality of Life Questionnaire for adults; HMA = haemophilia A; ; HMAwI = haemophilia A with inhibitors; HMB = haemophilia B; HMBwI = haemophilia B with inhibitors MC = multicentre; N = number of participants; N/A = not applicable; OL = open label; PPX = prophylaxis; RCT = randomised controlled trial; SF-36v2 = 36-item Short-Form Health Survey, version 2.
Source: adapted from Table 10 of MSAC 1805 ADAR + in-line commentary.

Explorer8 compared prophylactic treatment with concizumab against on-demand treatment with clotting factors in patients with HMA and HMB without inhibitors. The trial was an open-label RCT conducted across 31 countries (69 sites). The trial design and risk of bias in Explorer7 and Explorer8 were similar. Explorer8 included 2 randomised arms (1:2 ratio of control to

[3] Windyga J, Apte S, Frei-Jones M, Fujii T, Lyu CJ, Villarreal Martinez L, Sathar J, Stasyshyn O, Tran H, Zozulya N, Brown Frandsen R, Neergaard JS, Thaung Zaw JJ and Mahlangu J (2024) 'Disease and treatment burden of patients with haemophilia entering the explorer6 non-interventional study', *European Journal of Haematology*, 113(5):631–640, doi:10.1111/ejh.14277

Wheeler AP, Abraham A, Barnes C, Brown Frandsen R, d'Oiron R, Eichler H, Hampton K, López-Jaime FJ, Lyu CJ, Tavares CMM, Nogami K, Sutton C, Windyga J, Zulfikar B and Castaman G (2025) 'Real-World Unmet Needs of Patients With Haemophilia A and Haemophilia B With or Without Inhibitors: End-of-Study Results From the explorer6 Non-Interventional Study', *Haemophilia: The Official Journal of the World Federation of Hemophilia*, 31(5):903–911, doi:10.1111/hae.70051.

[4] Angchaisuksiri P, von Mackensen S, Apte S, Benson G, Eichler H, Findley A, Matsushita T, Mazini Tavares CM, Puggaard Ravn M, Sathar J, Villarreal Martinez L and Young G (2025) 'Concizumab prophylaxis in people with hemophilia A or B without inhibitors: patient-reported outcome results from the phase 3 explorer8 study', *Research and Practice in Thrombosis and Haemostasis*, 9(2):102705, doi:10.1016/j.rpth.2025.102705.

Chowdary P, Angchaisuksiri P, Apte S, Astermark J, Benson G, Chan AKC, Jiménez Yuste V, Matsushita T, Høgh Nielsen AR, Sathar J, Sutton C, Šaulytė Trakymienė S, Tran H, Villarreal Martinez L, Wheeler AP, Windyga J, Young G, Thaung Zaw JJ and Eichler H (2024) 'Concizumab prophylaxis in people with haemophilia A or haemophilia B without inhibitors (explorer8): a prospective, multicentre, open-label, randomised, phase 3a trial', *The Lancet. Haematology*, 11(12):e891–e904, doi:10.1016/S2352-3026(24)00307-7.

intervention) and 2 non-randomised arms (intervention) and, due to the open-label design, has some concerns for bias in the outcome measurement domain.

The comparator arm in Explorer8 is no prophylaxis, however the proposed population for concizumab is patients who require prophylaxis; therefore, the comparator in the trial has limited applicability to the clinical question and is only relevant for patients who may have refused IV prophylaxis but would be appropriate for, and willing to, commence subcutaneous prophylaxis. This would expand the eligible population.

For the main comparator, the ADAR used data from Explorer6 to conduct an intra-patient analysis comparing concizumab prophylaxis (Explorer7 data) with previous FIX prophylaxis (Explorer6). The analysis included 22 patients with HMB with a 3-week wash-out period between trials (Table 5).

Table 5 Summary of evidence base for each comparison in the HMB population

	Primary comparison – effectiveness	Secondary comparison – effectiveness	Safety
Comparator	FIX prophylaxis	On-demand FIX	FIX prophylaxis
Evidence base	Interrupted time-series of patients enrolled in Explorer6 (FIX prophylaxis) followed by Explorer8 (concizumab)	Open-label RCT (Explorer8) – Arm 1 (on-demand FIX) and Arm 2 (concizumab)	Open-label RCT including non-randomised arms and patients who crossed over from Arm 1 (Explorer8) – no comparator
Participants in analysis (n)	22 (all HMB)	36 (all HMB)	151 (HMA/HMB)

BPA = bypassing agent; FIX = Factor IX; HMA = haemophilia A; HMB = haemophilia B; RCT = randomised controlled trial.
Source: adapted from Table 11 of MSAC 1805 ADAR + in-line commentary.

Although the Explorer6, Explorer7 and Explorer8 trials are directly applicable, details of the comparator treatments (treatment type, dose, frequency, etc.) were not provided in the ADAR. The trials were conducted across many sites in multiple countries. Therefore, there is likely to be variability in current 'standard of care' across the trials and it may not be consistent with that in Australia.

The ADAR did not present data for all the outcomes listed in the PICO confirmation (responder status, other bleeding outcomes, individual bleed rate compared to historical bleed rate, perioperative use of therapy and outcomes, joint health outcomes, number of days or missed work/activity/school).

11. Comparative safety

The ADAR reported safety outcomes from the interventional arms of Explorer7 and Explorer8 trials only. Although both trials have very small comparator arms the ADAR did not present this data and the commentary considered they would be insufficient for the assessment of comparative safety. However, the commentary noted that in a population with severe haemophilia, bleeds tend to lead to the most serious adverse outcomes and therefore the ABR, which is the primary effectiveness outcome, also captures comparative safety to some extent.

The most common adverse events (AEs) reported in the trials as possibly or probably related to concizumab were injection-site reactions (48 events in 26 patients (20.5%) in Explorer7,

40 events in 23 patients (15.2%) in Explorer8). These were all mild, although in 1 patient injection-site pain led to permanent discontinuation of concizumab.

Two patients (1.6%) in Explorer7 had hypersensitivity reactions (1 non-serious, 1 serious) that led to permanent discontinuation of concizumab. The patient with a serious hypersensitivity reaction was also reported to have a history of hypersensitivity to FIX.

The AEs of hypersensitivity and injection-site reaction are expected to be specific to concizumab and its subcutaneous administration. AEs that are specific to FIX or BPA's, which require IV infusion, are not captured in the ADAR.

AEs leading to treatment discontinuation occurred in 6 participants (4.0% with 8 AEs) with HMA/HMB and 4 participants (3.1% with 4 AEs) with HMAwI/HMBwI. Serious AEs (SAEs) occurred in 14 participants (9.3% with 22 SAEs) with HMA/HMB and 14 participants (11% with 18 SAEs) with HMBwI/HMAwI.

Trial pause – thrombosis

Both the Explorer7 and Explorer8 trials underwent a treatment pause due to the occurrence of nonfatal thromboembolic events. A new dosing regimen was implemented upon re-initiation of the trial (the same as the dosing specified in the PICO confirmation), and any participants randomised before the pause were transferred to one of the non-randomised arms (3 or 4). For this reason, thrombosis was specified as a safety outcome by PASC.

The ADAR reported that:

- Prior to the study pause, one non-fatal, severe thromboembolic event (renal infarct) was reported in a patient with HMBwI (Explorer7).
- Prior to the study pause, 2 participants with HMA experienced 4 serious, nonfatal thromboembolic events (acute myocardial infarction, deep vein thrombosis, pulmonary embolism, superficial vein thrombosis) (Explorer8).

No thromboembolic events were reported after the trials restarted or in patients on no prophylaxis.

Anti-drug antibodies

In the HMAwI and HMBwI trial population, 33 (26%) out of the 127 patients exposed to concizumab were anti-drug antibody (ADA)-positive at 1 or more visits after first exposure to concizumab. Eight patients (6.3%) were positive for in vitro neutralising ADAs at 1 or more visits during the trial, with no apparent clinical impact.

In the HMA and HMB trial population, 18 (11.9%) out of the 151 patients exposed to concizumab were ADA-positive at 1 or more visits after first exposure to concizumab. Five patients (3.3%) were positive for in vitro neutralising ADAs at 1 or more visits during the trial, with no apparent clinical impact.

Conclusion regarding safety

The commentary noted that the data presented in the ADAR for safety were not comparative and were insufficient in sample size and follow-up to detect rare or late-onset AEs. Nevertheless, across the HMA and HMB population, with and without inhibitors, treated with concizumab, treatment-related AEs were most commonly mild injection-site reactions. No thromboembolic

events were reported after the trials restarted with revised dosing. Two hypersensitivity reactions were reported, both in patients with inhibitors, and these led to treatment discontinuation.

The ADAR concluded that the use of concizumab results in noninferior safety compared to standard of care for both comparisons. The commentary did not agree that this was supported by the evidence presented in the ADAR as it was non-comparative. Randomised trials of standard of care (BPAs and FIX) have been undertaken and could have been used to provide an indirect comparison of safety. Nevertheless, in the pivotal trials of concizumab, the most common AEs were mild injection-site reactions. The rate of more serious AEs, including those leading to treatment discontinuation, may be acceptable and consistent with a population with severe haemophilia.

12. Comparative effectiveness

Haemophilia B with inhibitors

Bleeding outcomes

Concizumab versus BPAs on demand

In adolescent and adult patients with haemophilia A or B with inhibitors, the Explorer7 RCT reported that the use of concizumab prophylaxis resulted in fewer treated spontaneous and traumatic bleeding episodes than the use of no concizumab (i.e. BPAs on demand). The ABR ratio was 0.14 in favour of concizumab (86% reduction, p<0.001) (Table 6). A statistically significant ABR ratio favouring concizumab was also reported for treated spontaneous bleeding episodes, treated spontaneous and traumatic joint bleeding episodes, all treated and untreated spontaneous and traumatic bleeding episodes, and for treated spontaneous and traumatic target joint bleeding episodes.

Table 6 Treated bleeding episodes in Explorer7 (HMAwI and HMBwI)

HMAwI & HMBwI	Concizumab prophylaxis (Arm 2 of Explorer7)	No concizumab prophylaxis (Arm 1 of Explorer7)	ABR ratio (95% CI)
Participants, n	33	19	-
Patients with zero treated bleeds, n (%)	5 (38.5)	1 (5.3)	-
Patients with treated bleeding episodes, n (%)	8 (61.5)	17 (89.5)	-
Number of treated bleeding episodes, n	25	167	-
Treated spontaneous and traumatic bleeding episodes – estimated mean ABR (95% CI)	1.7 (1.01, 2.87)	11.8 (7.03, 19.86)	0.14 (0.07, 0.29)

ABR = annualised bleeding rate; CI = confidence interval; HMAwI = haemophilia A with inhibitors; HMBwI = haemophilia B with inhibitors.
Source: adapted from Table 24 of MSAC 1805 ADAR + in-line commentary.

The ABR ratio for patients with HMBwI only for the primary outcome of treated traumatic and spontaneous bleeding episodes was 0.31 (95% CI 0.07 to 1.36; p = 0.120). The trial was not powered to detect differences within each haemophilia subtype.

Concizumab versus BPA prophylaxis

The ADAR included a post-hoc analysis to compare concizumab prophylaxis with BPA prophylaxis. The analysis included 7 patients with HMBwI who were on stable prophylaxis for at least 24 weeks in Explorer6 (details of prophylactic treatment were not reported) and who reached maintenance dose of concizumab in Explorer7. The ABR ratio favoured concizumab but was not statistically significant (Table 7). The ABR ratio for the HMAwI participants (0.16 [95% CI, 0.05 to 0.46], n=6) and the combined HMAwI/HMBwI participants (0.33 [95% CI, 0.15 to 0.72], n=13) were statistically significant. Due to the small number of participants, these results are prone to random variation and should be interpreted cautiously.

Table 7 Treated bleeding episodes in Explorer6 and Explorer7 intra-patient analysis (HMBwI)

HMBwI (n=7)	Concizumab prophylaxis (Arm 4 of Explorer7)	BPA prophylaxis (Explorer6)	ABR ratio (95% CI)
Treated spontaneous and traumatic bleeding episodes – estimated mean ABR	9.1 (2.58, 31.92)	18.1 (8.85, 37.18)	0.5 (0.23, 1.08)

ABR = annualised bleeding rate; BPA = bypassing agent; CI = confidence interval; HMBwI = haemophilia B with inhibitors.
Source: adapted from Commentary Table 24 of MSAC 1805 ADAR + in-line commentary.

Quality of life outcomes

Explorer7 measured a range of patient-reported outcomes (PROs); however, a considerable proportion of patients did not fill out the questionnaires. Therefore, the quality-of-life outcomes are at high risk of bias and have a reduced statistical power compared to bleeding outcomes.

For the combined group of patients with HMAwI and HMBwI, no differences were observed between concizumab prophylaxis and no prophylaxis for the 36-item Short-Form Health Survey Version 2 (SF-36v2) scores for bodily pain (Table 8) or physical functioning (not shown).

Table 8 SF-36v2 bodily pain outcomes for participants with HMAwI and HMBwI combined in Explorer7

Outcome	Concizumab prophylaxis	No prophylaxis	Difference estimate (95% CI)
SF-36v2 mean change in bodily pain from baseline to week 24 (95% CI)	9.2 (5.06, 13.25) [n=23]	2.2 (-5.14, 9.52) [n=9]	6.96 (-1.64, 15.57), p=0.109
Number of SF-36v2 responders at week 24 (at least 6.2 increase in bodily pain[a]), n/N (%)	2/12 (16.7%)	12/24 (50%)	-
SF-36v2 responders (at least 6.2 increase in bodily pain[a]) – estimated OR (95% CI)	1.1 (0.36 to 3.08)	0.3 (0.04 to 1.65)	4.12 (0.54, 31.71), p=0.174

CI = confidence interval; HMAwI = haemophilia A with inhibitors; HMBwI = haemophilia B with inhibitors; N = number of patients; OR = odds ratio; SF-36v2 = 36-item Short-Form Health Survey, version 2.
a. An increase of at least 6.2 in SF-36 bodily pain score was prespecified as the threshold for a clinically meaningful within-patient change.
Note: for SF-36v2, higher values indicate better functional health.
Source: adapted from Commentary Table 7 of MSAC 1805 ADAR + in-line commentary.

For the combined population of patients with HMAwI and HMBwI, there was a statistically significant difference, favouring concizumab, in mean change from baseline of the total score for the Haemophilia Quality of Life Questionnaire for adults (Haem-A-QoL; Table 9). The analysis was

based on 13 patients who received concizumab and 4 patients on no prophylaxis. No statistically significant improvement in the physical health domain score was observed (not shown).

Table 9 Haem-A-QoL total score – mean change from baseline for HMAwI and HMBwI participants in Explorer7

Outcome	Concizumab prophylaxis (n=13)	No prophylaxis (n=4)	Difference estimate (95% CI)
Mean Haem-A-QoL score at week 24 (95% CI)	32.4 (22.98, 41.88)	55.0 (37.75, 72.29)	-
Mean change from baseline to week 24 (95% CI)	-15.9 (-25.37, -6.47)	6.7 (-10.59, 23.95)	-22.6 (-42.46, -2.73), p=0.028

CI = confidence interval; Haem-A-QoL = Haemophilia Quality of Life Questionnaire for Adults; HMAwI = haemophilia A with inhibitors; HMBwI = haemophilia B with inhibitors.
For Haem-A-QOL, lower values indicate better quality of life.
Source: Commentary Table 6 of MSAC 1805 ADAR + in-line commentary.

Haemophilia B without inhibitors

Bleeding outcomes

Concizumab versus FIX prophylaxis

The Explorer8 RCT compared on-demand treatment against concizumab in HMB; however, in clinical practice, most Australian patients with severe or moderately severe HMB receive regular FIX prophylaxis. Data for this comparison was derived from the intra-patient analysis of 22 patients who were on stable prophylaxis for at least 24 weeks in Explorer6 (details of prophylactic treatment were not reported) and who reached maintenance dose of concizumab in Explorer8. Based on the ABR ratio of 1.75 (95% CI 0.81 to 3.78) noninferiority was not demonstrated as the upper bound of the CI exceeded the prespecified noninferiority margin of 2.0 that was predicted to preserve 60% of the established treatment effect of FIX prophylaxis. Noninferiority was also not confirmed in the HMA nor combined HMA/HMB (N=51) populations (ABR ratio 1.53 [95% CI 0.93 to 2.52]).

Table 10 Treated bleeding episodes in Explorer6 and Explorer8 intra-patient analysis (HMB)

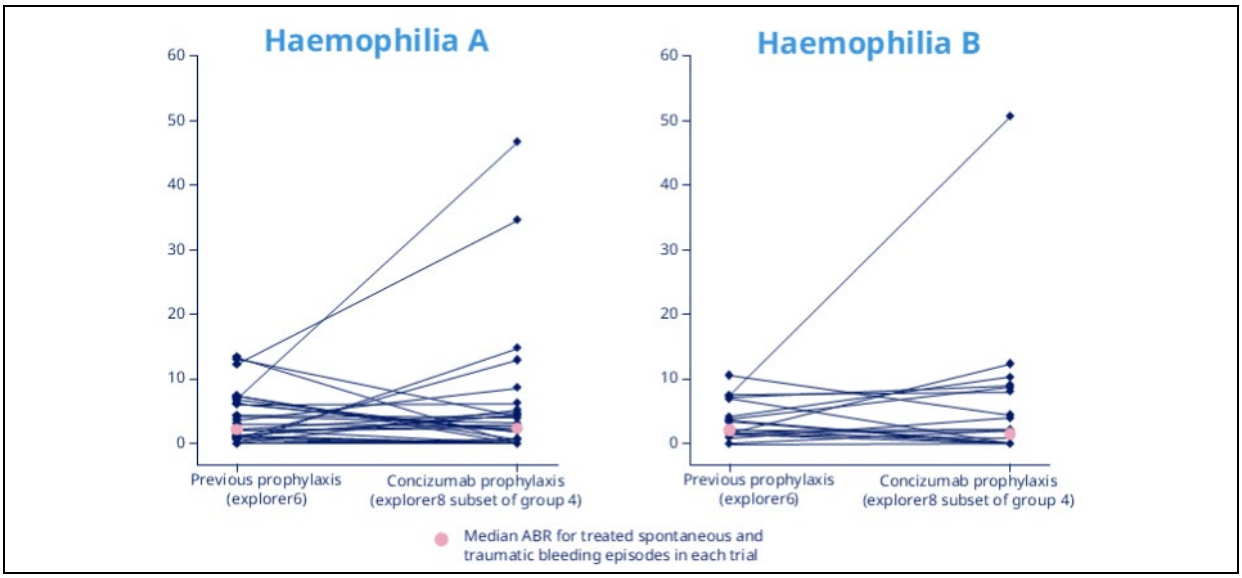
HMB (N=22)	Concizumab prophylaxis (Arm 4 of Explorer8)	FIX prophylaxis (Explorer6)	ABR ratio (95% CI)
Participants with zero treated spontaneous and traumatic bleeding episodes[a], n (%)	9 (40.9)	7 (31.8)	-
Treated spontaneous and traumatic bleeding episodes – estimated mean ABR (95% CI)	5.4 (2.27, 12.91)	3.1 (2.07, 4.62)	1.75 (0.81, 3.78)

ABR = annualised bleeding rate; CI = confidence interval; FIX = Factor IX; HMB = haemophilia B.
a. Also, no permanent discontinuation of treatment before 24 weeks.
Source: Table 16 of MSAC Application 1805 in-line Commentary.

The concizumab ABR for this analysis (Table 10) is influenced by an outlier patient who had an increased number of bleeding episodes on concizumab. A similar observation is made in the HMA population where 2 patients had a higher number of bleeds on concizumab prophylaxis. All 3 patients are visualised in Figure 1. The CSR stated that that all 3 patients remained on

concizumab for longer than necessary during the trial due to patient, family and/or investigator preference.

Figure 1 Treated spontaneous and traumatic bleeding episodes in patients with HMA and HMB in group 4 of Explorer8 (intra-patient analysis set)



Source: Supplementary Figure S3 of Chowdary et al. (2024). Creative Commons Licence CC BY 4.0.

The 3 patients are briefly described:

- HMB: 14-year-old with ABR of 50.6 on concizumab. Historically difficult to treat and engaged in sports with variable use of protective gear.
- HMA: 16-year-old with ABR of 46.7 on concizumab. Increased ABR attributed to worsening target joint/synovitis in the right ankle where all 11 treated bleeding episodes occurred. There were no bleeding episodes after synovectomy.
- HMA: 39-year-old with a mean ABR of 34 on concizumab. It was not possible to identify the specific cause of the high ABR during the trial.

The response of these patients may reflect random variation due to the small sample size but could also reflect variable response and reduced effectiveness in some patients. The ADAR presented a post-hoc analysis where the outlier HMB patient had values imputed, resulting in an ABR ratio of 1.00 (95% CI 0.58 to 1.73) that met the noninferiority margin. A tipping point analysis was also conducted that showed a reduction of 31 treated spontaneous and traumatic bleeding episodes is needed to change the noninferiority conclusion, corresponding to a reduction in the mean ABR estimate on concizumab prophylaxis from 5.4 to 3.8 and a reduction in the individual ABR of the outlier patient from 50.6 to 17.2. The commentary noted that this is a large change and that the use of imputed data is not adequately justified; however, it is recognised that HMB is a rare condition and that the trial reported difficulty recruiting the planned number of trial participants within a reasonable timeframe.

Concizumab versus FIX on demand

The randomised comparator in Explorer8 was on-demand treatment. The ABR ratio favoured concizumab over on-demand treatment (0.21 [95% CI 0.10 to 0.45]) (Table 11). A statistically significant ABR ratio in favour of concizumab was also reported for treated spontaneous bleeds, treated spontaneous and traumatic joint bleeds, and all treated and untreated spontaneous and traumatic bleeding episodes. The ABR ratio was not statistically significant for all treated

spontaneous and traumatic target joint episodes; because these occur at a lower frequency, this may reflect lack of statistical power. The findings in the HMA population from the randomised comparison with on-demand treatment were similar with an ABR ratio of 0.14 (95% CI 0.07 to 0.29).

Table 11 Treated bleeding episodes in Explorer8 (HMB)

HMB	Concizumab prophylaxis (Arm 2 of Explorer8) (n=24)	No concizumab prophylaxis (Arm 1 of Explorer8) (n=12)	ABR ratio (95% CI)
Participants with zero treated spontaneous and traumatic bleeds[a], n (%)	10 (41.7)	1 (8.3)	-
Patients with treated bleeding episodes, n (%)	17 (70.8)	11 (91.7)	-
Treated bleeding episodes, n	59	97	-
Treated spontaneous and traumatic bleeding episodes – estimated mean ABR (95% CI)	3.1 (1.91, 5.04)	14.8 (8.14, 26.86)	0.21 (0.10, 0.45), p<0.001

ABR = annualised bleeding rate; CI = confidence interval; HMB = haemophilia B.
a. Also, no permanent discontinuation of treatment before 24 weeks.
Source: Table 18 of MSAC Application 1805 in-line Commentary, Explorer8 CSR, narrative p155; Table 11-2, p123; and narrative p198.

Quality of life outcomes

Like Explorer7, Explorer8 measured a range of PROs with a similarly high proportion of non-response over the trial. Furthermore, the applicability of these outcomes is low, as Explorer8 compared concizumab prophylaxis to no prophylaxis, whereas the standard of care for patients with severe or moderately severe HMB is FIX prophylaxis.

A statistically significant difference was observed for the SF-36v2 bodily pain outcome in favour of concizumab (Table 12). No statistically significant difference in the odds ratio for achieving at least a 6.2-point increase in bodily pain score from baseline to week 24 was observed between patients in Arm 2 and Arm 1 (odds ratio 3.65 [95% CI 0.31, 43.42]). With the exception of the physical health component score, other domains of the SF-36v2 were not significantly different for the comparison of concizumab versus no prophylaxis; however, the direction of effect favoured concizumab.

Table 12 SF-36v2 bodily pain outcomes for HMB in Explorer8

Outcome	Concizumab prophylaxis (n=12)	No prophylaxis (n=6)	Difference estimate (95% CI)
SF-36v2 mean change in bodily pain from baseline to week 24 (95% CI)	-3.3 (-12.20, 5.69)	11.4 (4.89, 17.87)	14.64 (3.37, 25.91), p=0.014

CI = confidence interval; HMB = haemophilia B; N = number of patients; SF-36v2 = 36-item Short-Form Health Survey, version 2.
For SF-36v2, higher values indicate better functional health.
Source: Commentary Table 3 of MSAC Application 1805 in-line Commentary.

For the Haem-A-QoL questionnaire total score, there was a statistically significant difference between concizumab prophylaxis (n=11) and no prophylaxis (n=3), favouring concizumab (difference estimate -17.55 [95% CI -28.77 to -6.33]).

Clinical claim

For patients with HMB with inhibitors, the ADAR concluded that the use of concizumab results in:

1. Superior effectiveness compared with no prophylaxis (on-demand BPAs).

Superiority was not demonstrated for this comparison in the open-label RCT for the HMBwI population, however, the trial was underpowered for the HMBwI population alone. Superiority was demonstrated for the combined HMAwI/HMBwI population.

In summary, while the clinical claim of superiority made in the ADAR is supported by clinical evidence for the combined HMAwI and HMBwI populations, it is considered uncertain for HMBwI (GRADE certainty of evidence for HMBwI: Very low). The comparative effectiveness of concizumab may differ for the HMAwI and HMBwI populations. Patients with HMAwI have access to a broader range of treatments than patients with HMBwI, who tend to be restricted to rFVIIa, which introduces differences in comparative effectiveness for these populations compared to standard of care.

2. Superior effectiveness compared with BPA prophylaxis.

Superiority was not demonstrated in the intra-patient analysis for this comparison. The direction of effect favoured concizumab over BPA prophylaxis. Due to the small patient numbers and pre-post- design of the study, the commentary considered the clinical claim to be unsupported; however, a claim of noninferiority could be supported, albeit with a low level of certainty (GRADE certainty of evidence; Very low).

For patients with HMB without inhibitors, the ADAR concluded that the use of concizumab results in:

1. Noninferior effectiveness compared with FIX prophylaxis.

Noninferiority was not demonstrated for this comparison in the intra-patient analysis. Due to the small sample size, the analysis is prone to the influence of random variation. For this reason, the ADAR undertook an analysis replacing a patient with a high number of bleeds on concizumab with imputed data. The commentary does not consider this analysis to demonstrate noninferiority, noting that patients with high bleed numbers were also observed in the HMA population.

The commentary found that the clinical claim is not supported for the primary outcome (treated spontaneous and traumatic bleeds) as the true effects could include a higher ABR on concizumab than FIX prophylaxis. It is possible that variability in patient response is a contributing factor.

Although the commentary did not support the clinical claim of noninferiority for the primary outcome, the commentary noted the strong patient preference for a subcutaneous prophylactic treatment is acknowledged. Furthermore, it is noted that patients can be on concizumab prophylaxis and on-demand FIX. The volume of FIX used while patients were on concizumab prophylaxis was not reported in the ADAR. The commentary noted that patient preference and real-world considerations (access to on-demand treatment, patient compliance, burden on carers etc.) may still support an overall judgement of noninferiority, despite the data presented in the ADAR.

2. Superior effectiveness compared with no prophylaxis (on-demand FIX).

Superiority was demonstrated in the open-label RCT for this comparison for the HMB population (GRADE certainty of evidence: Low). The commentary noted that on-demand treatment is not standard of care for Australian patients with severe HMB.

13. Economic evaluation

A cost-minimisation analysis (CMA) was presented in the ADAR for both the HMB and HMBwI populations. Due to the claim of superiority for HMBwI over standard of care, the CMA for this population incorporated the cost of breakthrough bleeds.

Haemophilia B with inhibitors

The ADAR claimed that prophylactic concizumab is superior to standard of care and has presented a CMA approach so that funding is cost neutral to the health system. The ADAR did not explicitly address whether the introduction of concizumab is likely to lead to any other cost differences not accounted for in the CMA.

An overview of the CMA is provided in Table 13.

Table 13 Summary of the HMBwI economic evaluation

Component	Description
Therapeutic claim: effectiveness	The ADAR claimed superior effectiveness. The commentary considered the Explorer7 trial demonstrated superiority of concizumab over no PPX for a combined HMAwI and HMBwI population, but that the trial was not powered to detect a difference for the HMBwI population. Superiority was not demonstrated for the comparison against BPA PPX.
Therapeutic claim: safety	The ADAR claimed noninferior safety. The commentary considered that insufficient comparative safety evidence was presented; therefore, this claim is an assumption based on limited evidence and is uncertain.
Evidence base	Direct randomised trial (Explorer7) for the comparison of no prophylaxis.
Equi-effective doses	Concizumab: 0.212 mg/kg/day rFVIIa (NovoSeven®): 0.090 mg/kg/day
Direct health technology costs	Higher; $**redacted** (concizumab) versus $**redacted** (rFVIIa, including cost of prophylaxis and cost of rFVIIa on demand for breakthrough bleeding)
Other costs or cost offsets	Yes; cost of rFVIIa administration and cost offset of breakthrough bleeds.

ADAR = applicant-developed assessment report; BPA = bypassing agent; HMAwI = haemophilia A with inhibitors; HMBwI = haemophilia B with inhibitors; kg = kilograms; mg = milligrams; PPX = prophylaxis.
Source: Table 42 of MSAC Application 1805 in-line Commentary.

The ADAR assumed a 100% adherence rate for both the intervention and comparator, despite stating that treatment adherence is likely to be higher for subcutaneous concizumab compared to BPAs. The base case assumes 32% rFVIIa prophylaxis use over 1 year and on-demand treatment for the remainder of the year. The ADAR extrapolated use from Australian patients with HMBwI; however, year-on-year use varied, as did use between patients. Therefore, the cumulative time on rFVIIa prophylaxis per year is uncertain and likely to vary depending on individual patient factors. Given the very small sample size, individual patient variation would directly impact the overall cost neutrality.

The ADAR has included administration costs for rFVIIa due to it being administered by IV infusion. The cost is based on an outpatient hospital setting and is applied to all infusions. The commentary noted that patients can self-infuse, and it is unclear what proportion of infusions would occur in a healthcare setting versus at home. No administration costs are included for concizumab.

Similarly, the ADAR has applied a cost for each treated bleeding episode based on an inpatient hospitalisation. The commentary considered that this may lead to an overestimation of treatment costs. In Explorer7, approximately 90% of bleeds in HMBwI participants were categorised as mild or moderate and by definition do not require hospitalisation.

The total cost per year of each treatment in the ADAR base case is presented in Table 14. This is a cost per milligram of $**redacted** for concizumab compared to $1,250.00 for rFVIIa.

Table 14 Total cost per patient for a year of treatment

Item	Concizumab	rFVIIa
Drug cost (prophylaxis)	**redacted**	$**redacted**
Administration cost for prophylaxis	$0	$56,309
Breakthrough bleeding – rFVIIa cost	$0	$372,555
Breakthrough bleeding – hospitalisation cost (includes administration)	$26,923	$76,289
Total cost per patient per year	$**redacted**	$**redacted**

Source: Table 49 of MSAC Application 1805 in-line Commentary.

Key drivers of the analysis were the duration of BPA prophylaxis, the inclusion of rFVIIa costs in the intervention arm, and the adherence rates for each treatment (Table 15).

Table 15 Key drivers of the analysis

Description	Method/Value	Impact Base case: $redacted/mg
Duration of BPA prophylaxis	Extrapolated from **redacted** patients for base case of 32% per year. Sensitivity analysis at 25% (3 months) and 50% (6 months).	*High* *Use of 25% decreased the cost to $**redacted**/mg.* *Use of 50% increased the cost to $**redacted**/mg.*
Inclusion of rFVIIa cost for breakthrough bleeds in the concizumab arm	The cost of rFVIIa for the treatment of breakthough bleeds when patients are on prophylactic concizumab is to be covered by NovoNordisk and therefore was not included in the CMA.	*High* *Favours concizumab* *Inclusion of these costs decreased the cost to $**redacted**/mg.*
Higher adherence for concizumab compared to rFVIIa	Base case assumed 100% adherence for both treatments. However, rFVIIa is predicted to have poorer adherence (87.2% based on reference to FIX).	*High* *Favours concizumab* *Different adherence rates decreased the cost to $**redacted**/mg.*

CMA = cost minimisation analysis; BPA = bypassing agent; FIX = Factor IX; mg = milligram.
Source: Compiled by commentary for the executive summary.

The results of key univariate sensitivity analyses are summarised in Table 16.

Table 16 Key sensitivity analyses

Scenario	Cost per unit of concizumab to be cost neutral	Change in concizumab per unit to base case
Base case	**$redacted**	**-**
Including the cost of on-demand rFVIIa in concizumab arm	**$redacted**	-**$redacted**
Proportion of time on rFVIIa prophylaxis 50% (6 months)	**$redacted**	**$redacted**
Proportion of time on rFVIIa prophylaxis 25% (3 months)	**$redacted**	-**$redacted**
BPA ABRs reported in Explorer6 (Wheeler et al. 2025)	**$redacted**	-**$redacted**
No difference in ABRs	**$redacted**	-**$redacted**
No administration cost for rFVIIa	**$redacted**	-**$redacted**
No cost for bleeds (above drug cost)	**$redacted**	-**$redacted**
Adherence higher for concizumab	**$redacted**	-**$redacted**

ABR = annualised bleeding rate; BPA = bypassing agent.
Source: adapted from Table 52 of MSAC Application 1805 in-line Commentary.

The commentary undertook a scenario analysis using the following inputs:

- Lower adherence for rFVIIa (87%) compared to concizumab (100%)
- Including the cost of rFVIIa in the concizumab arm
- ABRs for BPAs as reported in Explorer6 (Wheeler et al. 2025)
  - 9.3 for HMBwI on demand
  - 12.4 for HMBwI on prophylaxis
- Breakthrough bleeding hospitalisation costs applied to 10% of bleeds.

The analysis results in a cost per mg of concizumab of $**redacted** (Table 17). PASC advised the approach to this economic evaluation needed to consider the lack of an established cost-effectiveness for the BPA treatments. This was not addressed in the ADAR and remains a source of uncertainty in terms of whether the proposed cost-neutral price is also a cost-effective price.

Table 17 Results of scenario analysis using inputs proposed by the commentary

Item	Concizumab	rFVIIa
Drug cost (prophylaxis)	**$redacted**	**$redacted**
Administration cost for prophylaxis	$0	$49,101
Breakthrough bleeding – rFVIIa cost	$131,480	$314,696
Breakthrough bleeding – hospitalisation cost (includes administration)	$2,692	$6,444
Total cost per patient per year	**$redacted**	**$redacted**
Cost per mg	**$redacted**	$1,250.00

mg = milligram.
Source: Commentary Table 9 of MSAC Application 1805 in-line Commentary.

The results of the revised cost-minimisation analysis based on ESC's specifications (Table 29) is presented in Table 18.

Table 18 Revised cost-minimisation analysis based on total cost per patient for a year of treatment

Item	Concizumab	rFVIIa
Administration cost for prophylaxis	$**redacted**	$0[a]
Breakthrough bleeding – rFVIIa cost [b]	$77,530	$253,735
Breakthrough bleeding – hospitalisation cost (includes administration) [c]	$13,775	$45,081
Total cost per patient per year	$**redacted**	$**redacted**
Cost per mg	$**redacted**	$1,250.00

Source: Calculated by the Department based on ESC's specifications.
[a] No rFVIIa prophylaxis (comparator is on-demand treatment).
[b] Based on annualised bleed rates of 7.2 (HMBwI patients previously using on-demand treatment) and 2.2 on concizumab. Cost of treating a bleed was $**redacted** based on **redacted** mg of rFVIIa per bleeding event (**redacted** mg/kg for a **redacted** kg patient).
[c] Hospitalisation cost of $6,261.24 per bleed.

Haemophilia B without inhibitors

An overview of the CMA is provided in Table 19. Although the conclusion of the clinical claim was uncertain, given the small patient population and the reported patient preference for a subcutaneous treatment option, a cost minimisation approach for the analysis of HMB without inhibitors is reasonable. However, if bleed rates are higher with concizumab compared to FIX prophylaxis (albeit offset by patient preference), a cost-utility analysis would be more informative.

Table 19 Summary of the HMB economic evaluation

Component	Description
Therapeutic claim: effectiveness	The ADAR claimed noninferior effectiveness. The commentary considered the clinical evidence did not meet the prespecified noninferiority margin and therefore there remains uncertainty regarding the clinical claim of noninferiority compared to FIX PPX.
Therapeutic claim: safety	The ADAR claimed noninferior safety. The commentary considered that insufficient comparative safety evidence was presented; therefore, this claim is an assumption based on limited evidence and is uncertain.
Evidence base	The clinical evidence to inform the FIX PPX comparator is an intra-patient before-and-after analysis (observational Explorer6 trial and non-randomised arms of Explorer8 trial)
Equi-effective doses	Concizumab 0.213 mg/kg/day FIX replacement: Alprolix® 50 IU/kg/weekly, BeneFIX® 40 IU/kg twice weekly, MonoFIX-VF® 32.5 IU/kg twice weekly
Direct health technology costs	Higher; $**redacted**(concizumab) versus $**redacted**(FIX)
Other costs or cost offsets	Yes; cost of FIX administration

ADAR = Applicant developed assessment report; FIX = Factor IX; IU = international units; kg = kilograms; mg = milligrams; PPX = prophylaxis.
Source: Table 31 of MSAC Application 1805 in-line Commentary.

The assumptions consistent with the HMBwI analysis were:

- A 100% adherence rate for both the intervention and comparator, despite ADAR statement that treatment adherence is likely to be higher for subcutaneous concizumab compared to FIX.
- Included administration costs for FIX based on an outpatient hospital setting.

The utilisation of FIX product, and product mix, is based on data from the Australian Bleeding Disorders Registry (ABDR); however, data were only available until 2021-22 and were highly variable. Therefore, this is a source of uncertainty and is likely to change over time, particularly as new products are introduced.

The total cost per year of each treatment in the ADAR base case is presented Table 20. This is a cost per milligram of $**redacted** for concizumab compared to $**redacted** per IU for FIX replacement.

Table 20 Total cost per patient for a year of treatment

Item	Concizumab	FIX replacement
Drug cost	$**redacted**	$**redacted**
Administration	$0	$33,863
Total cost per patient	$**redacted**	$**redacted**

FIX = Factor IX.
Source: Table 38 of MSAC Application 1805 in-line Commentary.

Key drivers of the analysis were the price of FIX, the inclusion of administration costs for FIX and the adherence rates for FIX compared to concizumab (Table 21).

Table 21 Key drivers of the analysis

Description	Method/Value	Impact Base case: $redacted/mg
MonoFIX-VF® published price used for all FIX products	The price of MonoFIX-VR® based on the National Product Price List is $1.09 per IU. The prices of BeneFIX® and Alprolix® are confidential and were estimated at $1.50 per IU for Alprolix® and $0.85 per IU for BeneFIX®.	*High* *Favours concizumab* *Use of MonoFIX-VF® price decreased the cost to* $**redacted***/mg.*
Cost of administration of FIX excluded	The cost of administration was included and based on an outpatient hospital setting. Most patients self-infuse FIX.	*High* *Favours concizumab* *Exclusion of these costs decreased the cost to* $**redacted***/mg.*
Higher adherence for concizumab compared to FIX	Base case assumed 100% adherence for both treatments. However, FIX is predicted to have poorer adherence (87.2%).	*High* *Favours concizumab* *Different adherence rates decreased the cost to* $**redacted***/mg.*

FIX = Factor IX; IU = international units; mg = milligrams.
Source: Compiled by commentary for the executive summary.

The results of key univariate sensitivity analyses are summarised in Table 22. In a scenario analysis where all 3 variables are modified (MonoFIX-VF® price, exclusion of administration costs, variable adherence), the cost per unit of concizumab is $**redacted**.

Table 22 Key sensitivity analyses

Scenario	Cost per unit of concizumab to be cost neutral	Change in concizumab cost per unit to base case
Base case	**$redacted**	**-**
Alprolix® and BeneFIX® treatment costs matched to MonoFIX-VF® published price	$**redacted**	-$**redacted**
Administration costs excluded (self-administered)	$**redacted**	-$**redacted**
Adherence higher for concizumab (100%; 87.2% for comparators)	$**redacted**	-$**redacted**

Source: adapted from Table 41 of MSAC Application 1805 in-line Commentary.

MSAC also considered an analysis based on Table 29.

14. Financial/budgetary impacts

A combined epidemiology and market-share approach was used to estimate the financial impact of the proposed inclusion of concizumab in the NPPL under the National Blood Agreement for the HMB population.

Haemophilia B with inhibitors

The ADAR reported there are currently **redacted** patients in Australia that have HMBwI and are eligible for concizumab. In the financial analysis, this was assumed to remain constant over the first 6 years. The actual number of patients is likely to vary year to year, and the commentary observed that a small change in patient numbers (i.e. the addition or loss of **redacted** patients) would impact the cost substantially.

Using the cost-neutral prices generated in the CMA of $**redacted**/mg, the financial implications to the national blood arrangements resulting from the proposed listing of concizumab are summarised in Table 23. This is proposed to be offset by the reduced use of rFVIIa for prophylaxis and on-demand treatment.

Table 23 Net financial implications of concizumab prophylaxis for patients with HMBwI

Parameter	Year 2027	Year 2028	Year 2029	Year 2030	Year 2031	Year 2032
Estimated use and cost of the proposed health technology						
Number of patients eligible for concizumab (patients with HMBwI receiving PPX)	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Number of patients who receive concizumab	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Doses administered	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Cost to the NBA	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**
Change in use and cost of other health technologies						
Change in use of rFVIIa prophylaxis – number of doses	-**redacted**	-**redacted**	-**redacted**	-**redacted**	-**redacted**	-**redacted**
Administration cost to hospitals	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**
Drug cost to NBA	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**
Change in use of rFVIIa on demand – number of doses	-**redacted**	-**redacted**	-**redacted**	-**redacted**	-**redacted**	-**redacted**
Administration cost to hospitals	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**
Drug cost to NBA	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**
Net financial impact to the NBA	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**
Net financial impact to hospitals	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**

HMBwI = haemophilia B with inhibitors; NBA = National Blood Authority; PPX = prophylaxis.
Source: adapted from Tables 64, 65, and 66, of MSAC Application 1805 in-line Commentary.

The financial analysis is informed by the CMA and therefore subject to the same sensitivities. The commentary considered the greatest uncertainty in the model to be the extent of prophylactic BPA use currently in eligible patients, noting this is likely to vary between patients and across time. As the drug is indicated for long-term, daily prophylactic treatment, the cost to the National Blood Agreement of concizumab would be substantial despite the very small patient population.

Haemophilia B without inhibitors

The eligible population was derived from the ABDR using the number of patients with HMB on prophylaxis. The commentary noted this represents patients currently on prophylaxis and may not represent all who are eligible for prophylaxis. Uptake of prophylaxis may be expected to increase if a subcutaneous treatment is available. In 2023–24, there were 116 patients with HMB in the ABDR with severe disease; 140 with moderate disease and 328 with mild disease. Therefore, there is scope for expansion of the population eligible for uptake of concizumab prophylaxis. Conversely, uptake of gene therapy could reduce the eligible population, given it is intended as a one-time treatment to eliminate the requirement for regular prophylaxis. Furthermore, market share for concizumab could be affected by other subcutaneous treatments entering the market.

The ADAR estimated uptake of concizumab to be redacted% in the first year of listing, growing to and plateauing at redacted% by Year 4. The ADAR stated this was a conservative estimate; however, a lower uptake assumption results in a higher weighted price. Patient preference data indicated strong patient preference for subcutaneous administration over current injection methods, and rapid and high uptake of emicizumab in the HMA population supports this assertion.

Using the cost-neutral price generated in the CMA of $redacted, the financial implications to the National Blood Agreement resulting from the proposed listing of concizumab for HMB are summarised in Table 24.

Table 24 Net financial implications of concizumab for prophylaxis in HMB

Parameter	Year 2027	Year 2028	Year 2029	Year 2030	Year 2031	Year 2032
Estimated use and cost of the proposed health technology						
Number of patients eligible for concizumab (patients with HMB receiving PPX)	redacted	redacted	redacted	redacted	redacted	redacted
Number of patients who receive concizumab	redacted	redacted	redacted	redacted	redacted	redacted
Doses administered	redacted	redacted	redacted	redacted	redacted	redacted
Cost to the NBA	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Change in use and cost of other health technologies						
Change in use of Alprolix® (number of patients)	-redacted	-redacted	-redacted	-redacted	-redacted	-redacted
Change in use of BeneFIX® (number of patients)	-redacted	-redacted	-redacted	-redacted	-redacted	-redacted
Change in use of MonoFIX-	redacted	redacted	redacted	redacted	redacted	redacted

Parameter	Year 2027	Year 2028	Year 2029	Year 2030	Year 2031	Year 2032
Estimated use and cost of the proposed health technology						
VF® (number of patients)						
Change in use of Alprolix® (number of doses)	-redacted	-redacted	-redacted	-redacted	-redacted	-redacted
Change in use of BeneFIX® (number of doses)	-redacted	-redacted	-redacted	-redacted	-redacted	-redacted
Cost to the NBA - Alprolix®	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted
Cost to the NBA – BeneFIX®	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted
Administration cost to hospitals – Alprolix®	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted
Administration cost to hospitals – BeneFIX®	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted
Net financial impact to the NBA	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Net financial impact to hospitals	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted

HMB = haemophilia B; NBA = National Blood Authority; PPX = prophylaxis.
Source: adapted from Table 57, 59 and 60 of MSAC Application 1805 in-line Commentary.

The commentary considered the main uncertainty to be the degree of uptake of concizumab, which is likely to be underestimated due to both the potential for uptake by patients not currently on prophylactic therapy and patient preference for subcutaneous therapy. Uptake in patients not currently on FIX prophylaxis could affect cost neutrality.

A further uncertainty for future financial impact is the assumption that the current therapies are replaced in the historical average proportions. Given that new therapies have been only recently approved for market in Australia, this assumption is unlikely to hold but is highly uncertain.

Table 25 Higher uptake scenario and impact on cost of concizumab to the National Blood Agreement

Item	2027	2028	2029	2030	2031	2032
Adult patients with HMB receiving prophylactic treatment	redacted	redacted	redacted	redacted	redacted	redacted
Uptake rate	redacted%	redacted%	redacted%	redacted%	redacted%	redacted%
Concizumab treated patients	redacted	redacted	redacted	redacted	redacted	redacted
Doses administered	redacted	redacted	redacted	redacted	redacted	redacted
Administration cost to hospitals	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Drug cost to NBA	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted

HMB = haemophilia B; NBA = National Blood Authority.
Source: Commentary Table 14 of MSAC Application 1805 in-line Commentary.

Weighted price analysis

A weighted cost per unit of concizumab was calculated in the ADAR based on the relative use of concizumab for HMB and HMBwI over 6 years.

Table 26 Concizumab price based on relative use for HMB and HMBwI over 6 years

Population	Number of patient-years over 6 years	Units per year per patient (mg)	Total units over 6 years (mg)	Proportion of use	Cost per unit	Annual cost per patient (using unweighted price)	Annual cost per patient (using weighted price)
HMB	redacted	redacted	redacted	redacted%	$redacted	$redacted	$redacted
HMBwI	redacted	redacted	redacted	redacted%	$redacted	$redacted	$redacted
Weighted			redacted		$redacted	$redacted	

HMB = haemophilia B; HMBwI = haemophilia B with inhibitors; mg = milligrams.
Source: Table 53 of MSAC Application 1805 in-line commentary.

Due to the difference in cost per unit for the 2 populations, an increased uptake in patients with HMB results in a decreased weighted cost per unit.

Table 27 Impact of higher proportion of patients with HMB compared to HMBwI on the weighted price

Item	Base	Scenario 1	Scenario 2
HMB proportion of use	redacted%	redacted%	redacted%
Weighted cost	$redacted	$redacted	$redacted

HMB = haemophilia B; HMBwI = haemophilia B with inhibitors.
Source: Commentary Table 10 of MSAC Application 1805 in-line Commentary.

Applying the weighted price of $redacted (Table 26) to the financial analysis results in no net overall cost over 6 years. However, the projected difference in the rate of concizumab uptake across the 2 indications means the budget impact fluctuates within the 6-year period.

Table 28 Overall budget impact of concizumab for HMB and HMBwI (weighted price)

Item	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Concizumab cost to NBA for HMB	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Concizumab cost to NBA for HMBwI	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Total cost of concizumab to the NBA	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Total cost of FIX therapy replaced	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted
Total cost of rFVIIa therapy replaced	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted
Net cost to the NBA	-$redacted	-$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Net cost to hospitals	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted
Net impact to government health budgets	-$redacted	-$redacted	-$redacted	$redacted	$redacted	$redacted	$0

FIX = Factor IX; HMB = haemophilia B; HMBwI = haemophilia B with inhibitors; NBA = National Blood Authority.
Source: Table 68 of MSAC Application 1805 in-line Commentary.

MSAC also considered an analysis based on Table 29.

15. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The application is seeking funding for all patients with haemophilia B (HMB) (with or without inhibitors) >12 years of age, which is broader than the clinical trial evidence for patients without inhibitors that was restricted to severe or moderate-severe disease.
- ESC agreed with the commentary that on-demand treatment with activated recombinant Factor VII (rFVIIa) (no prophylaxis) should be the main comparator for HMBwI, not short-term prophylaxis as proposed by the applicant. ESC agreed that for the HMB without inhibitors population the main comparator should be prophylaxis with Factor IX (FIX).
- The comparators used in the clinical evaluation (and by extension the economic evaluation) may not reflect current Australian standard of care (SOC). In particular, extended half-life (EHL) FIX has largely replaced standard half-life (SHL) FIX in Australia. However, the clinical effectiveness outcomes reported for the HMB without inhibitors population are based on a likely larger proportion of SHL prophylaxis used as SOC at participating sites at the time of the Explorer6 observational study. ESC noted that the ADAR did not provide details on treatments received by participants in the comparator arms, making it unclear whether concizumab was compared with a representative SOC, and that variation across jurisdictions and study sites may further limit the applicability of the findings to the Australian setting.
- Several near market (Marstacimab (MSAC Application 1806, under consideration in this cycle); etranacogene dezaparvovec (MSAC Application 1728.1, supported, not funded for use yet) and new-to-market comparators (albutrepenonacog alfa, Idelvion®) are likely to influence the treatment landscape of HMB in Australia. None of these has been considered in the ADAR, despite the ratified PICO Confirmation requesting this.
- The safety data were not comparative and were limited in both sample size (i.e. number of participants) and duration of follow-up. Accordingly, the claim of noninferior safety compared with SOC was not clearly demonstrated for either the HMB with inhibitors (HMBwI) or HMB without inhibitors population.
- For the HMBwI population, ESC did not accept the claim that concizumab demonstrated superior effectiveness compared with on-demand rFVIIa. Although the evidence base included a randomised comparison, the superiority claim relied on pooled data from patients with haemophilia A with inhibitors (HMAwI) and HMBwI. While the combined analysis showed a statistically significant reduction in annualised bleeding rate (ABR) in favour of concizumab, this finding was not maintained when the analysis was restricted to the HMBwI population. Although the point estimates still favoured concizumab (ABR 2.2 vs 7.2), the ABR ratio of 0.31 was associated with wide confidence intervals that crossed unity (95% CI: 0.07 to 1.36). The claim of superior effectiveness compared with short-term rFVIIa prophylaxis was also not supported. The evidence base for this comparison comprised a post-hoc intra-patient before-and-after analysis of seven study participants which ESC considered to be of low-confidence.
- For the HMB without inhibitors population, ESC did not support the clinical claim of noninferior effectiveness compared with FIX prophylaxis. The ABR ratio (concizumab versus FIX prophylaxis, post-hoc intra-patient before-and-after analysis) in the HMB without inhibitors population did not support the noninferiority claim. Rather, the point estimates for ABR ratio suggested that concizumab may be inferior to the comparator. Superiority compared with on-demand FIX was demonstrated; however, this

comparison is of limited relevance as on-demand FIX is not considered the SOC for patients with severe HMB.

Economic issues:

- ESC recommended that a more conservative approach was warranted for the cost-minimisation approach (CMA) adopted in the application, given low confidence in the clinical evidence and the sensitivity of the economic evaluation to several key structural and input assumptions which were based on this evidence. In particular, ESC recommended that the economic evaluations for both populations should be respecified assuming 87.2% adherence to prophylaxis treatments in the comparator arm (as opposed to 100% adherence in the ADAR). For the HMBwI population, ESC also recommended that it would be more appropriate to assume that rFVIIa is only used for on-demand treatment rather than also including short-term prophylaxis,
- ESC recommended that the CMA for the HMB without inhibitors population should be respecified to take account of cost offsets from a lower ABR in the comparator arm given that point estimates for ABR suggest that concizumab may be inferior to the comparator in that population.
- Although the applicant proposed covering the costs of breakthrough bleeds through rFVIIa supply for all patients with HMBwI receiving concizumab and used this to justify excluding these costs from the CMA, ESC advised that as all base case economic evaluations to MSAC should take a health system perspective (regardless of payer), the costs of managing breakthrough bleeds should be included in the concizumab arm.

Financial issues:

- The proposed financial impact is presented as being cost-neutral across both populations; however, this outcome is highly dependent on key modelling assumptions, including uptake rates, population size, substitution patterns, dosing and cost offsets. If these assumptions are not realised in practice, cost neutrality may not be achieved and net costs to the health system may arise. This risk is mitigated by ESC's advice to adopt a more conservative approach for the CMA.
- The financial analysis assumes immediate 100% substitution of rFVIIa for redacted patients with HMBwI and uptake increasing to redacted% by year 6 for redacted HMB without inhibitors patients receiving FIX prophylaxis. ESC considered there may be some delay in substitution by patients with HMBwI, and noted clinical advice suggesting this population may be approximately 4-times larger (~redacted patients), creating further uncertainty in projected costs.
- Uptake in the HMB population without inhibitors may exceed the redacted% assumed, as demonstrated after the introduction of emicizumab (subcutaneous therapy) for HMA. Higher than expected anticipated uptake of concizumab would materially affect expenditure and would reduce the weighted average price calculated across the two populations.
- The financial analysis assumes use is limited to patients already receiving FIX prophylaxis, however, in practice, use may extend to a broader HMB population, increasing financial risk.
- To manage financial risk from the significant uptake and cost uncertainties, if concizumab is supported for public funding ESC considered a risk share agreement (RSA) with a high rebate for use above the subsidisation/financial cap is likely unsuitable due to market complexity and multiple competing products. ESC considered that price negotiation, and/or an alternative RSA based on concizumab cost per patient and administration costs, would be more appropriate.

ESC Discussion

ESC noted that this application from Novo Nordisk requested listing on the National Blood Authority's (NBA's) National Product Price List (NPPL) of concizumab (Alhemo®) for patients ≥12 years of age with congenital haemophilia B (HMB), with (HMBwI) or without inhibitors, who require prophylaxis. ESC noted that concizumab is currently approved by the Therapeutic Goods Administration (TGA) for use in both haemophilia A (HMA) and haemophilia B (HMB) and in patients with or without inhibitors.

ESC noted that the Therapeutic Goods Administration (TGA) registration does not specify any disease severity category for either HMB with or without inhibitors, but there is an age restriction for both of ≥12 years of age. However, the studies leading to registration in HMB without inhibitors were restricted to individuals with severe or moderate-severe disease. For HMB with inhibitors (HMBwI), the study leading to registration was not restricted by disease severity (owing to an absence of effective long-term prophylaxis options).

Concizumab is a monoclonal antibody that targets tissue factor pathway inhibitor (TFPI), a regulator of the coagulation process. By binding to TFPI, concizumab enhances coagulation through directly preventing Factor Xa (FXa) inhibition and indirectly preventing activated Factor VII (FVIIa) inhibition. As concizumab's mechanism of action is independent of Factor IX (FIX) and Factor FVIII (FVIII), its effectiveness is not affected by the presence of inhibitors to these factors.

ESC noted that public consultation input was received from 4 organisations: 3 peak bodies (including a consumer group) and the Australian Haemophilia Centre Directors' Organisation (AHCDO). ESC noted that all the feedback was received before the PASC deliberation and no new feedback was received for ESC. ESC noted that overall the feedback was generally supportive, indicating that listing concizumab would be meaningful to both the HMA and HMB patient populations, particularly for patients with high treatment burden and persistent unmet need. ESC further noted feedback that patients experience a high burden of care, including cumulative physical damage, chronic pain and psychosocial stress, and that the complexity and intrusiveness of long-term management remain a concern for people with these conditions.

ESC noted that the AHCDO identified no implementation barriers, although AHCDO noted that patients who meet the eligibility criteria for concizumab and have not had experience with it will need to be educated on administration and monitoring of effectiveness and safety. ESC further noted feedback from the Haemophilia Foundation of Australia (HFA) which highlighted that participants from a clinical trial of concizumab had positive feedback about the therapy. ESC further noted feedback from both organisations that the subcutaneous administration of concizumab offered an important advantage over intravenous therapy, particularly in relation to venous access, treatment fatigue and day-to-day independence.

ESC noted additional feedback that, compared with other treatments in this class, the proposed therapy does not require ongoing cold-chain storage. ESC considered that this reduces the practical burden on families and provides greater flexibility for travel and participation in daily activities, which may support quality of life and treatment adherence. However, ESC acknowledged potential equity concerns, particularly regarding the practicality of ensuring ongoing specialist oversight, especially in rural, remote and lower-income settings. Regarding environmental considerations, ESC noted that there was a negative impact due to the treatment being a single-use device, which may increase plastic waste, but considered that this was potentially offset through other benefits of treatment such as fewer hospital admissions and reduced emergency transport.

ESC noted that patients with HMBwI have a higher clinical need for this treatment than those without inhibitors, as no long-term prophylaxis treatments are currently available for patients with HMBwI.

ESC noted that the recommended dosing regimen comprises an initial loading dose followed by a standard maintenance dose. Four weeks after treatment initiation, a trough (i.e. pre-dose) concizumab plasma concentration is measured once by a concizumab-specific enzyme-linked immunoassay (ELISA). The result of this test is used to determine the individualised maintenance dose.

ESC considered the proposed clinical management algorithm to be appropriate. ESC noted that patients with severe HMB or moderate HMB without inhibitors typically receive routine intravenous FIX prophylaxis. ESC noted that, for patients with HMBwI, clinical management depends on the inhibitor titre levels. For patients with low-titre HMBwI, treatment may involve increasing the dosage of FIX replacement therapy. For patients with high-titre HMBwI no long-term prophylaxis option is available. For acute bleeds in patients with HMBwI and high-titre inhibitors and/or allergic reactions to factor products, a bypassing agent (BPA) is used. ESC noted that the two BPAs available in Australia are recombinant activated Factor VIIa (rFVIIa) and activated prothrombin complex concentrate (aPCC), and noted that aPCC is generally not preferred in HMB due to the presence of FIX, which may increase the risk of anaphylaxis.

ESC noted that the ADAR proposed that the main comparator for HMBwI should be short-term prophylaxis with bypassing agents (BPAs) and that on-demand treatment with BPAs (no prophylaxis) should be the secondary comparator. ESC noted and agreed with the commentary that on-demand treatment with BPAs (no prophylaxis), in this case rFVIIa, is the most appropriate comparator given that BPAs are only indicated for short-term prophylaxis (≤3 months) in situations where bleeding risk is increased (such as perioperative use) whereas concizumab is indicated for long-term prophylaxis.

ESC noted that the comparator for HMB without inhibitors is FIX prophylaxis which is the current standard of care (SOC) in Australia for patients with HMB. The current clinical management for these patients involves prophylaxis with extended half-life (EHL) recombinant FIX (Alprolix®), which is replacing prophylaxis with standard half-life (SHL) recombinant FIX (BeneFIX®), both of which have largely replaced plasma-derived SHL FIX (MonoFIX-VF®) in Australia.

ESC noted that albutrepenonacog alfa, Idelvion®, an EHL recombinant FIX product, has been on the NPPL as part of the National Blood Agreement since June 2025 and agreed with the commentary that it could have been included as a new to market near-comparator; however, as it has only been available since July 2025, uptake is difficult to predict with precision. ESC considered that although a sensitivity analysis modelling potential switching from Alprolix® to Idelvion® over time could be undertaken, switching would be expected primarily where a previously stable patient with Alprolix® develops breakthrough bleeding. ESC further considered that, as MSAC had previously advised no price differential across EHL FIX products (MSAC PSD for 1511, page 4), the relative extent of use of these products should not affect the cost-minimisation approach (CMA) in the economic and financial analyses.

ESC further noted that etranacogene dezaparvovec, Hemgenix®, which was supported for funding by MSAC at its July 2025 meeting, is a therapy available for the treatment of adult patients with moderately severe or severe HMB (see MSAC Application 1728.1 PSD) and is a near-market comparator as is, marstacimab, which is TGA-registered and concurrently under consideration by MSAC to treat patients with severe HMA or HMB without inhibitors (Application 1806). ESC noted that the applicant-developed assessment report (ADAR) did not include either of these therapies as a comparator for concizumab, despite this being requested by PASC.

ESC noted that the main clinical effectiveness outcome in the evidence for both populations was the annualised bleeding rate (ABR). The ADAR presented no comparative safety data. ESC considered that the ABR is established as a primary outcome for registration studies, but was not necessarily an accepted patient-relevant outcome, and noted that it could also be viewed as a safety endpoint.

ESC noted that the clinical evidence for the effectiveness of concizumab for the HMBwI population was informed by 2 studies:

- Explorer6 – a non-interventional pre-trial cohort study of patients with severe HMA, severe/moderate HMB without inhibitors, or any severity of HMA with inhibitors (HMAwI) or HMBwI (a total of 31 patients with HMBwI)
- Explorer7 – a randomised controlled trial (RCT) of patients with HMAwI or HMBwI (some of whom participated in Explorer6) treated with BPAs in the 24 weeks before screening (a total of 25 patients with HMBwI [15 for the intervention and 10 for the comparator]).

ESC noted that the Explorer7 study was the pivotal study for the HMBwI population in this application, as it included the appropriate comparator of on-demand treatment with rFVIIa. Consistent with the discussion above regarding comparators, ESC acknowledged that the ADAR identified on-demand rFVIIa as a secondary comparator and had noted some short-term rFVIIa prophylaxis was supported by real-world data. However, ESC queried whether sufficient real-world data had been provided to justify short-term rFVIIa prophylaxis as the main comparator. In the absence of further evidence, ESC affirmed that on-demand rFVIIa should be the primary comparator for this population.

ESC noted that the ADAR assessed the risk of bias for Explorer6 as moderate using the Cochrane risk of bias tool for non-randomised studies of interventions (ROBINS-I). However, ESC noted from the commentary that the ROBINS-I tool has limited utility for a non-interventional, single-arm study such as Explorer6. ESC also raised concerns regarding the risk of bias for Explorer7 due to the lack of information on the randomisation method and allocation concealment.

ESC noted that in the Explorer7 trial, the mean ABR for the pooled population (HMAwI and HMBwI) was 1.7 (95% confidence interval [CI]: 1.01, 2.87) for the intervention (concizumab prophylaxis) and 11.8 (95% CI: 7.03, 19.86) for the comparator (no concizumab prophylaxis), equating to an ABR ratio of 0.14 (95% CI: 0.07, 0.29) and demonstrating superiority for concizumab. ESC noted that, in its pre-ESC response, the applicant justified pooling the HMAwI and HMBwI populations due to the rarity of the conditions and the similar mechanism of action of concizumab. However, ESC noted from the supplementary Appendix for the Explorer7 trial report[5] that restricting the analysis to the HMBwI population reduced certainty in the superiority of the intervention because, although the point estimates still favoured concizumab (mean ABR of 2.2 vs 7.2), the corresponding ABR ratio of 0.31 had wide confidence intervals that crossed unity (95% CI: 0.07, 1.36). This also contrasted with the HMAwI population which had an ABR ratio of 0.09 with narrower confidence intervals (95% CI: 0.04, 0.18). ESC also noted that the baseline ABR in the no prophylaxis arm differed between the 2 populations (18.3 for HMAwI and 7.2 for HMBwI), suggesting pooling of data may not be appropriate.

ESC noted that total quality-of-life (QoL) scores from the Explorer7 trial showed superiority for concizumab. However, ESC noted that substantial data were missing, with QoL reported for only

[5] Matsushita T, Shapiro A, Abraham A, Angchaisuksiri P, Castaman G, Cepo K, d'Oiron R, Frei-Jones M, Goh A-S, Haaning J, Hald Jacobsen S, Mahlangu J, Mathias M, Nogami K, Skovgaard Rasmussen J, Stasyshyn O, Tran H, Vilchevska K, Villarreal Martinez L, Windyga J, You CW, Zozulya N, Zulfikar B and Jiménez-Yuste V (2023) 'Phase 3 Trial of Concizumab in Hemophilia with Inhibitors' [Supplemental Material], *New England Journal of Medicine*, 389(9):783–794, doi:10.1056/NEJMoa2216455.

13 of 33 patients in the intervention arm and 4 of 19 patients in the comparator arm. Therefore, although the superiority finding was statistically significant (p = 0.028), ESC considered the result unreliable.

ESC noted the ADAR's clinical claim for patients with HMBwI is that concizumab has superior effectiveness compared to no prophylaxis. However, ESC considered overall that these findings are subject to low confidence due to very small patient numbers and limitations in the evidence base discussed. ESC noted that the claim of superior effectiveness compared with short term rFVIIa prophylaxis is subject to even lower confidence, being based on a post-hoc intra-patient before-and-after comparison of seven study participants.

ESC noted that the clinical evidence for the effectiveness of concizumab for the HMB without inhibitors population was also informed by 2 studies:

- Explorer6 – described previously; a total of 72 patients with HMB without inhibitors
- Explorer8 – an RCT of patients with severe HMA or severe/moderate HMB without inhibitors and, unless transferring from Explorer5, with documented clotting factor treatment in the 24 weeks before screening (a total of 36 patients with HMB without inhibitors [24 for the intervention and 12 for the comparator]).

ESC noted that the ADAR combined data from the 2 studies to perform a within-person before-and-after analysis, described in the ADAR as an 'interrupted time series', involving 22 patients with HMB without inhibitors.

ESC noted concern from the commentary regarding the applicability of the comparator used in Explorer6 to Australian clinical practice. ESC noted that in the pre-ESC response, the applicant acknowledged regional variances exist with treatment, but that international principles guide individualised pharmacokinetic-guided dosing. However, ESC considered that the applicability to the Australian setting remained uncertain, because EHL FIX prophylaxis, rather than SHL FIX prophylaxis, represents current standard of care (SOC) for Australian patients with HMB ESC noted that the comparator in the Explorer8 trial was not relevant for this application, as it used no prophylaxis rather than FIX prophylaxis. ESC noted that the clinical claim of superior effectiveness compared with on-demand FIX was demonstrated, but considered that this comparison is of limited relevance because on-demand FIX is not considered SOC for patients with severe HMB.

ESC noted that the ADAR identified some concerns regarding the risk of bias for Explorer8. ESC also noted that the commentary highlighted a higher risk of bias for health-related QoL outcomes due to a higher patient drop-out rate, and that treatment pause may be considered a deviation from the intended intervention.

ESC noted that a post-hoc intra-patient analysis of ABR in Explorer6 versus Explorer8 showed between patient variability in response to the intervention vs the comparator, with one outlier patient experiencing substantially higher bleeding rates on concizumab. ESC also noted that the mean ABR ratio of 1.75 (95% CI: 0.81, 3.78) did not support the noninferiority claim for the intervention. The ADAR argued that removing the outlier produced a noninferior finding (ABR ratio of 1.00 [95% CI: 0.58, 1.73]); however, ESC noted that the commentary identified this outlier was not an isolated case, as the HMA trial population also included 2 outliers with markedly worse outcomes using concizumab compared with the comparator. Therefore, ESC considered that removing the outlier from the data was unjustified.

ESC considered that, given the comparator from Explorer6 observational study reflected local SOC at the time across diverse locations, and that EHL FIX has recently replaced SHL FIX as SOC in Australia, the comparative effectiveness of concizumab may be overestimated. ESC noted that at the time MSAC considered EHL prophylaxis, (MSAC Application 1511) the evidence showed

there was little clinically important difference between EHL and SHL prophylaxis, more recent accumulating observational evidence suggests EHL is superior to SHL, as measured by ABR reduction and adherence to treatment. [6,7,8,9] ESC considered that an assessment of recent evidence (since MSAC 1511 consideration) of the effectiveness of SHL and EHL products would be informative to MSAC. Overall, ESC considered the ADAR's claim of noninferior effectiveness of concizumab in the HMB without inhibitors population was not supported by the evidence, although ESC acknowledged potential patient preference for concizumab over FIX prophylaxis.

Regarding the safety of concizumab, ESC noted that the ADAR presented non-comparative safety data with limited sample size and follow-up. The most common treatment related AEs with concizumab were mild injection-site reactions; two hypersensitivity reactions in patients with inhibitors led to discontinuation, and no thromboembolic events were reported. ESC also noted that the ADAR's claims of noninferior safety versus SOC for both HMB and HMBwI populations were not demonstrated, although serious AEs were infrequent and the overall safety profile appeared acceptable for patients with severe haemophilia.

ESC noted that the economic evaluation used a cost-minimisation approach (CMA) for both populations and calculated the cost-neutral concizumab shadow price on a per patient per year basis. Specifics for each population as presented in the ADAR are as follows:

- For HMBwI
  - Fewer bleeds in the concizumab arm were valued as cost offsets but not as health outcome gains (consistent with the CMA)
  - Costs per patient in the comparator arm were based on comparisons with both on-demand rFVIIa to manage bleeding events and rFVIIa prophylaxis
  - Cost offsets of rFVIIa administration due to subcutaneous administration in the concizumab arm were included
  - A cost-neutral shadow price of $redacted/mg was estimated based on a total cost per patient per year of $redacted for concizumab (which would offset a cost of the same magnitude under standard of care).
- For HMB without inhibitors
  - Cost offsets for fewer bleeds in the concizumab arm were not included (due to the assumption of noninferior effectiveness in this population)
  - Costs per patient in the comparator arm were weighted across 3 FIX products (all with different costs per patient)
  - Cost offsets of FIX prophylaxis administration due to subcutaneous administration in the concizumab arm were included
  - A cost-neutral shadow price of $redacted/mg was estimated based on a total cost per patient per year of $redacted for concizumab.

[6] Brennan Y, Parikh S, McRae S and Tran H (2020) 'The Australian experience with switching to extended half-life factor VIII and IX concentrates: on behalf of the Australian Haemophilia Centre Directors' Organisation', *Haemophilia*, 26(3):529–535.

[7] George C, Parikh S, Carter T, Mccosker J, Carlino S and Tran H (2023) 'Evaluation of treatment and outcome for patients with haemophilia A and haemophilia B on extended half-life (EHL) factor products: a 12-month data analysis', *Haemophilia*, 29(5):1283–1290.

[8] Koivusalo M, Szanto T, Kovalainen T, Vesikansa A, Laine O, Partanen A et al. (2025) 'Switching from standard to extended half-life coagulation factor replacement in haemophilia: clinical outcomes and costs of care in Finland', *Haemophilia*, 31(4):722–733.

[9] Bidlingmaier C, Heller C, Langer F, Miesbach W, Scholz U, Oldenburg J et al. (2024) 'Real-world usage and effectiveness of recombinant factor VIII/factor IX Fc in hemophilia A/B: final data from the 24-month, prospective, noninterventional PREVENT study in Germany', *Research and Practice in Thrombosis and Haemostasis*, 8(5):102482.

ESC agreed with the commentary that the lack of an established cost-effectiveness for rFVIIa in the economic evaluation is a source of uncertainty regarding whether the proposed cost-neutral price for concizumab represents an acceptable cost-effective price. ESC noted that the CMA for both populations relied on assumptions of clinical equivalence supported by low-confidence evidence. ESC considered that, for the HMBwI population, small sample size and wide confidence intervals limited certainty regarding the magnitude of benefit, and for the HMB without inhibitors population, noninferiority to standard prophylaxis was not demonstrated, with evidence based on a small before-and-after comparison rather than a robust assessment against contemporary Australian practice. ESC noted that the economic models were sensitive to several key structural and input assumptions which were based on this low-confidence evidence.

ESC noted that there are multiple treatments currently available for haemophilia and emphasised the importance of consistency across the comparable parameters used in the economic evaluations for these products. ESC recommended that, in this context, a conservative approach to pricing is warranted when confidence in a parameter is low and multiple quantifiable alternative estimates are reasonable, accepting that some remaining parameters do not have obvious alternative estimates. ESC further recommended that uncertainty in clinical benefit should be reflected through a lower acceptable cost-neutral price, rather than assuming parity with existing therapies, with price negotiation serving as the primary mechanism to also manage financial risk. ESC also noted MSAC precedents for previous blood replacement products which adopted this approach and acknowledged that this applies to assumptions regarding daily doses in prophylaxis and adherence (assumed in the CMA to be 100% for all prophylactic treatments) for both HMB groups.

For the HMBwI population, ESC noted that the applicant proposed that the cost of managing breakthrough bleeds in the concizumab arm through prophylaxis should be assumed to be zero in the CMA because the applicant proposed covering the costs for breakthrough bleeds through the supply of rFVIIa for all patients with HMBwI receiving concizumab. ESC considered that this approach raised practical, ethical, privacy and policy issues for the NBA and healthcare workers in haemophilia treatment centres. ESC also considered that, as the economic evaluation should consider costs from a health system perspective regardless of payer, all relevant costs should be included in the analyses. Therefore, ESC advised that the cost of managing breakthrough bleeds through rFVIIa should be included in the concizumab arm and the claimed cost-neutral price of concizumab adjusted accordingly. ESC further considered that, although the applicant's proposal to cover the costs for ELISA testing might appear to raise similar issues, this was acceptable as such funding would enable TGA-approved access rather than being a prerequisite for public funding.

ESC noted a discrepancy in the dosing of the rFVIIa used to treat breakthrough bleeds in the Explorer7 trial. The applicant cited a dose of 0.295 mg/kg in both the ADAR and pre-ESC response; however, ESC noted that the commentary was unable to identify this figure in the trial reference material and proposed a higher dose of 0.340 mg/kg based on data provided in the trial, which ESC considered to be more appropriate. ESC emphasised that accurate costing of breakthrough bleed management was important, as this parameter materially affected the comparator costs and the resulting cost-neutral price.

ESC therefore recommended that the base case of each of the two CMAs be respecified for MSAC consideration according to Table 29.

Table 29 ESC-recommended multivariate respecifications for recalculating the CMAs

Variable	Proposed product	Comparator	Rationale
Cost-minimisation approach (CMA) with inhibitors			
Product cost	*Back-calculated to achieve cost-neutrality*	1. Multiply by adherence at 87.2% 2. Remove 32% on prophylaxis leaving 100% on demand	1. Observed for FIX[3] 2. Reflect strongest randomised trial data generating breakthrough bleed estimates
ABR to estimate number of breakthrough bleeds	2.2	7.2	Relevant subgroup analysis from randomised comparison in Explorer7
rFVIIa cost for treating breakthrough bleeds	Include at 0.340mg/kg	Include at 0.340mg/kg	Accept Table 14.2.34, p320, Explorer7 CSR
Hospital and administration cost for treating breakthrough bleeds	Include	Include	Accept 1728.1 precedent of hospital and administration offsets in calculating cost neutrality
Cost-minimisation approach (CMA) without inhibitors			
Product cost	*Back-calculated to achieve cost-neutrality*	1. Use cheapest EHL FIX based on TGA-approved dose and in-confidence NBA unit price 2. Multiply by adherence at 87.2%	1. Consistency with MSAC recommendation for no cost differential between EHL FIX products (PSD for 1511, page 4) 2. Observed for FIX[3]
Administration cost of product	$0	1. 50% self- administered (i.e. no administration cost) and 50% nurse administered at $375.96/administration 2. Adjusted for number of doses administered 3. Two additional sensitivity analyses should also be undertaken assuming 100% self-administration costs (i.e. zero administration costs) and 100% of administration costs comprising nurse administered costs.	1. Nurse administration cost represents 2025-26 national efficient price from IHPA for code 40.48 (for IV infusion by a nurse) 2. Consistency with product cost and 1728.1 precedent
ABR to estimate number of breakthrough bleeds	5.4	3.1	Relevant post hoc subgroup analysis of intra-patient comparison across Explorer6 and Explorer8
EHL FIX cost for treating breakthrough bleeds	Use cheapest EHL FIX based on TGA-approved dose for a moderate bleed and NBA data to estimate number of doses/bleed and in-confidence NBA unit price	Use cheapest EHL FIX based on TGA-approved dose for a moderate bleed and NBA data to estimate number of doses/bleed and in-confidence NBA unit price. ESC recommended an assumption of 130 IU/kg/patient/bleed.	Consistency with MSAC recommendation for no cost differential between EHL FIX products (PSD for 1511, page 4) The assumption of 130 IU/kg/patient/bleed is

			based on the Australian Bleeding Disorders Registry Annual Report 2023-24 which reported this as the average IU/kg per patient for on-demand use across all severity inclusive of all **initial and subsequent doses**. ESC noted that this assumption triangulates well with 60 IU/kg as the approximate midpoint recommended for **initial** doses in the Alproplix Product Information (specifically the PI recommends an initial dose of 30-60 IU/kg for mild to moderate bleeds and 100 IU/kg for severe bleeds).
Hospital and administration cost for treating breakthrough bleeds	Include	Include	Accept 1728.1 precedent of hospital and administration offsets in calculating cost neutrality

ESC noted that the CMA for the HMBwI population included cost offsets for reduced hospitalisations associated with breakthrough bleeding costs. ESC considered that one residual source of uncertainty associated with accepting hospitalisation costs without more detailed scrutiny of these costs was that there was potential for costs associated with rFVIIa treatment of these bleeds to be double counted because the hospitalisation cost data should include treatment costs.

ESC noted that the financial estimates incorporated all calculated costs and cost offsets to maintain cost neutrality across both HMBwI and HMB without inhibitors populations. ESC noted the financial analysis assumed immediate 100% substitution for all **redacted** estimated patients with HMBwI and immediate substitution of **redacted**% to **redacted**% for an increasing population (**redacted** patients) patients with HMB without inhibitors receiving FIX prophylaxis. ESC considered immediate substitution unlikely, although this would be partially offset by the immediate reduced use of comparator therapies. ESC also noted that clinical expert opinion received by PASC estimated the HMBwI population to be **redacted** patients rather than **redacted**. ESC noted that the requested concizumab price was weighted average based on the projected total funded cost over 6 years across both populations ($**redacted**/mg). ESC noted that if all calculations are accepted, this would result in net savings in years 1 to 3 (fewer patients with HMB without inhibitors) and net costs in all years thereafter.

ESC noted that the financial analysis assumed concizumab uptake of approximately **redacted**% of the eligible HMB without inhibitors population, but advised that a higher uptake of **redacted**% should be assumed in the financial analysis to reflect the strong patient preference for subcutaneous administration which would be consistent with the higher than anticipated uptake of subcutaneous treatment in HMA following the introduction of emicizumab (see MSAC Application 1510.1). ESC noted that the financial estimates assume concizumab would be taken

up by patients previously receiving FIX prophylaxis, but ESC considered that in practice it may also be taken up by patients with HMB not currently receiving FIX.

ESC therefore recommended that the base case of the financial analysis be respecified for MSAC consideration, incorporating the results of the respecified CMAs and the additional respecifications according to the table below.

Table 30 Additional ESC-recommended multivariate respecifications for recalculating the financial analysis

Variable	Proposed product	Comparator	Rationale
Number of eligible patients with inhibitors	Increase gradually from **redacted** to **redacted** patients over 6 years	Leave at **redacted** patients	Expert advice to PASC that there are **redacted** eligible patients, likely receiving non-NBA funded interventions
Uptake by eligible patients with inhibitors	100% each year	100% substitution each year for **redacted** patients only	Accept application's rationale
Per patient per year costs of patients with inhibitors	As for relevant respecified CMA above, including the back-calculated shadow prices of concizumab in each population	As for relevant respecified CMA above	Consistency across economic and financial analyses
Uptake by eligible patients without inhibitors	Increase to **redacted**% rather than **redacted**%, retaining similar proportional increases each year as in application	Increase consistent with concizumab	Expert advice to PASC of likely uptake; accept application's rationale for substitution
Per patient per year costs of patients without inhibitors	As for relevant respecified CMA above, including the back-calculated shadow prices of concizumab in each population	As for relevant respecified CMA above	Consistency across economic and financial analyses
Recalculate weighted average price across 6 years			

Regarding the potential for leakage, if public funding for concizumab is supported ESC considered that a risk-share agreement with a high rebate for use above the subsidisation/financial cap was inappropriate because of the complexity of the market (requiring a HMA and HMB market) and the number of products. ESC considered a price negotiation would be more appropriate. In addition, there could be a risk-share agreement based on the total annual cost per patient and total administration costs. ESC noted that the NBA has governance in place to minimise leakage, which has been successful for previously funded products.

ESC requested that the respecified multivariate analyses of the economic and financial analyses be undertaken prior to MSAC to inform MSAC's consideration.

16. Applicant comments on MSAC's Public Summary Document

Novo Nordisk welcomes MSAC's support for funding concizumab for patients with Haemophilia B with inhibitors (HMBwI), recognising the significant unmet need in this ultra-rare population, and the role of concizumab as the first ongoing prophylactic treatment option. Although BPAs are not intended for long-term prophylaxis and MSAC accepted concizumab as a long-term prophylactic therapy, the pricing approach did not adequately reflect this, with an episodic on-demand care framework applied instead. Novo Nordisk does not consider this appropriate and remains

committed to working constructively with the Department to secure timely patient access through a fair and sustainable pricing arrangement.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website