Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1806 – Marstacimab for routine prophylaxis to prevent bleeding in patients with Haemophilia

Applicant: **Pfizer Australia Pty Ltd**

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

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application was received by the Department of Health, Disability and Ageing, from Pfizer Australia Pty Ltd, requesting Hympavzi® (subsequently referred to as marstacimab) be publicly funded under the National Blood Agreement via listing on the National Product Price List (NPPL), to prevent bleeding in patients with severe Haemophilia A (HMA) and Haemophilia B (HMB), who are without Factor VIII and Factor IX inhibitors (respectively).

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 did not support public funding of marstacimab for routine prophylaxis to prevent bleeding in either patients with congenital haemophilia A (HMA) without inhibitors or congenital haemophilia B (HMB) without inhibitors.

MSAC considered there is a clinical need for subcutaneous treatment for the HMB population, however identified that there is currently a number of intravenous treatment options available for this population. MSAC noted in the main trials comparing marstacimab to factor prophylaxis for patients with HMB (BASIS and BASIS LTE), patients mainly used standard half-life (SHL) factor prophylaxis which does not reflect contemporary Australian clinical practice, where most Australian patients use extended half-life (EHL) factor prophylaxis. MSAC considered this made the safety and efficacy results presented in the main trials less applicable to the Australian population. MSAC considered that the use of SHL factor replacement in the main trial cohort likely overestimates the benefit of marstacimab. Therefore, MSAC considered there was significant uncertainty in the safety and effectiveness claims of marstacimab compared to factor prophylaxis in the HMB population. In the analysis of marstacimab compared to emicizumab for patients with HMA, MSAC was unable to substantiate the claim of non-inferior safety and effectiveness, due to critical differences between the BASIS (marstacimab) and HAVEN 3 (emicizumab) trials. MSAC considered the indirect treatment comparison of the studies were subject to differences in treatment practices across countries and changes in treatment practice over time, and unmeasured confounding, which caused uncertainty in the results.

MSAC noted that the uncertainty in the comparative safety and effectiveness of marstacimab created high uncertainty in the economic analyses. MSAC also noted the lack of established cost-effectiveness basis for existing therapies, and the requirement in the MSAC Guidelines 2021 for cost-effectiveness to be established for the comparator (TG 2.3). Therefore, MSAC considered it could not determine the incremental cost effectiveness of marstacimab. MSAC also considered

this presented a significant risk for the financial analysis, despite it appearing to result in a potentially low overall financial cost. MSAC considered that a resubmission would require evidence that demonstrates the comparative safety and effectiveness of marstacimab, in both or either population, that is generalisable to the Australian clinical setting.

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 Pfizer Australia requested listing of marstacimab on the National Blood Authority's National Product Price List for the treatment of people aged 12 years or over with severe haemophilia A or haemophilia B, without inhibitors.

Haemophilia A and haemophilia B are inherited bleeding conditions where a person's blood does not clot properly. People with haemophilia lack certain proteins, called blood clotting factors, that are needed for blood to clot properly. Specifically, people with haemophilia A have low levels of Factor VIII [8] and people with haemophilia B have low levels of Factor IX [9]. The low levels of Factor VIII or Factor IX is commonly caused by a variation in the gene that codes these proteins. People with haemophilia bleed for longer than usual and may have sudden, painful bleeding in their joints or muscles.

Haemophilia is usually treated by replacing the missing blood clotting factors, through either an injection of the therapies into a vein (intravenous) or into tissue just under the skin (subcutaneous). Treatment can be given regularly to help prevent bleeding (prophylaxis) or given when bleeding occurs (on demand). In rare cases, people with haemophilia can develop inhibitors, which means their immune system starts producing antibodies (inhibitors) that target the replacement factor products and prevent the treatment from working. This application is for people with haemophilia A or B who do not have inhibitors.

Several prophylaxis treatment options are already available for patients with haemophilia who do not have inhibitors. These include emicizumab which mimics the role of Factor VIII (given via subcutaneous injection) only for patients with HMA, and factor replacement (given via intravenous injection) which can used in patients with HMA or HMB. This application proposed the use of marstacimab, given weekly via subcutaneous injection, instead of emicizumab or factor replacement. Marstacimab works by enhancing an alternative clotting pathway that uses a different clotting factor (Factor X) to help blood clot properly and bypassing the need for Factor VIII or IX.

MSAC considered the clinical studies had several issues that made the results less reliable. This included small patient numbers, differences between how the studies were conducted and differences between the study population and the Australian haemophilia population. In particular, most patients in the studies used standard half-life clotting factor. Most Australian patients use extended half-life clotting factor – which may be better at preventing bleeds. These issues meant that MSAC could not be certain that marstacimab was as safe, or effective, as emicizumab or factor replacement prophylaxis.

MSAC also considered that the application should have compared marstacimab with concizumab and etranacogene dezaparvovec, which are alternative treatments that can be used for patients with haemophilia B without inhibitors. However, these other treatments are not yet available public funded treatments but have been considered by MSAC (see MSAC applications 1805 and 1728.1).

MSAC noted that the uncertainties with the evidence base carried through to the economic and financial evaluation. Because of this, MSAC could not be certain that marstacimab was good value for money. MSAC also considered that, because marstacimab is a subcutaneous injection, more people may prefer it over intravenous injections, meaning uptake (and therefore costs) could be higher than estimated.

Consumer summary
MSAC's advice to the Commonwealth Minister for Health, Disability and Ageing MSAC did not support listing marstacimab on the National Product Price List for the treatment of people with severe haemophilia A or haemophilia B, without inhibitors. MSAC considered there were significant uncertainties with the evidence base, and MSAC could not be certain that marstacimab was as effective or safe as other treatments, nor that it was good value for money.

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

MSAC noted that this application from Pfizer Australia Pty Ltd requested listing of marstacimab on the National Blood Authority (NBA) National Product Price List (NPPL) for the treatment (routine prophylaxis) of people aged 12 years or over with severe haemophilia A (HMA) or severe haemophilia B (HMB), without inhibitors. MSAC noted that marstacimab is registered on the Australian Register of Therapeutic Goods (ARTG) solely for this population and does not have regulatory approval for any other populations (for example, children under the age of 12, patients with inhibitors, or patients with less severe disease).

MSAC noted that consultation input was generally supportive of listing marstacimab. MSAC noted the input highlighted that marstacimab offers a subcutaneous treatment option to patients, through a weekly application of a fixed dose using a pen device. MSAC noted consumers felt there was a significant treatment burden due to the frequent need to administer medication, including intravenously for some patients. MSAC noted the input that this provides convenience, ease of access and can improve patient quality of life (QoL). MSAC noted that the feedback was particularly supportive for patients with HMB, who at the time of consideration, did not have a publicly funded subcutaneous treatment option.

MSAC noted that the evidence base for marstacimab versus Factor VIII (FVIII) prophylaxis and Factor IX (FIX) prophylaxis consisted of a small, non-randomised, open-label, before-and-after case series of patients with HMA and HMB using self-reported outcomes during 12 months of treatment (BASIS), and an extension of this study with 34.9-month follow up (BASIS LTE). For the comparison of marstacimab to emicizumab in the HMA population, MSAC noted the evidence for emicizumab versus prophylaxis consisted of another small, non-randomised, open-label, before-and-after case series, also using self-reported outcomes (HAVEN 3).

MSAC agreed with ESC that the BASIS and BASIS LTE studies had significant limitations and considered that there was a high risk of bias. MSAC also agreed with ESC that the generalisability of the studies to the Australian population was uncertain, due to the difference in treatment regimens in the studies compared to Australian clinical practice. MSAC noted most patients in the BASIS studies received standard half-life (SHL) factor products, whereas most people with haemophilia in Australia receive extended half-life (EHL) products.

MSAC noted a key issue from ESC was that new evidence suggested that EHL products may be superior to SHL products. However, the applicant's pre-MSAC response asserted the new evidence was insufficient to conclude EHL products were superior as the evidence was of a low quality, similar to evidence considered by MSAC when it previously assessed EHL blood clotting factors VIII + IX for Haemophilia A and B (MSAC application 1511). MSAC recalled that application 1511 presented a small volume of low-quality evidence from two systematic reviews; one of which was an indirect comparison of SHL and EHL products, and one matched adjusted

indirect comparison of SHL and EHL products. MSAC recalled that the evidence in MSAC application 1511 showed small improvements to annual bleed rates (ABR), and a small increase in quality of life when using EHL products compared to SHL products. However, at that time, MSAC had concluded that while there may be incremental benefits associated with EHL products, the presence of incremental benefit was uncertain and any incremental benefit appeared to be small. MSAC noted that the new evidence was observational Australian patient data which supports the benefits for EHL compared to SHL products that were noted by MSAC when it previously considered MSAC application 1511. MSAC agreed with ESC that the recent accumulating observational evidence for Australian patients, suggest EHL products may be superior to SHL products[1,2,3,4]. Therefore, MSAC considered that by comparing marstacimab to SHL (the factor prophylaxis used by the majority of patients in BASIS) the incremental effectiveness of marstacimab may be over-estimated compared to the incremental effectiveness that would likely be observed in practice in Australia.

MSAC noted an ongoing clinical trial, expected to be completed in 2027, that is evaluating the impact of changing therapy from emicizumab to marstacimab in patients with severe HMA. MSAC noted this trial is an open labelled, non-randomised, within-patient comparison study and has a small number of participants (10-15). Given these characteristics, MSAC considered that this study is unlikely to have a substantial impact for future decision-making relating to the population with HMA without inhibitors who are already able to be treated with emicizumab. This trial may provide evidence of benefit for the expected small number of patients receiving emicizumab that develop neutralising anti-emicizumab antibodies.

MSAC noted the applicant developed assessment report (ADAR) claimed marstacimab had non-inferior safety compared to emicizumab in the HMA population. MSAC noted the indirect comparison between HAVEN 3 and BASIS to determine safety against emicizumab did not adjust for differences between the studies. These include heterogeneity in assessment methods, timing and reporting of safety outcomes, and different median treatment exposure times. MSAC considered that this caused significant uncertainty in the results of the safety comparison. MSAC noted the comparison showed the number of serious adverse events (SAEs), treatment-related SAEs and discontinuations due to adverse events (AEs) were similar for marstacimab and emicizumab. While MSAC noted that the evidence did show safety was likely non-inferior, due to the uncertainty in the outcomes, MSAC considered the safety claim could not be supported by the evidence presented.

MSAC noted the ADAR claimed marstacimab had non-inferior safety compared to EHL FIX prophylaxis in the HMB population. MSAC noted that the analysis of the safety outcomes was conducted using data from a pooled HMA and HMB population. MSAC noted that there was a small increase of adverse events (AEs) in the marstacimab group compared to those using factor prophylaxis, however the overall AEs were mild-moderate in severity. MSAC noted that the pre-

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[1] 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.

[2] 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

[3] 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

[4] 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.

MSAC response defended the pooling of HMA and HMB data, stating that the mechanism of action is the same for HMA and HMB, and that this means there is no biological basis for expecting differing results in the HMA and HMB populations. The applicant also stated that combining the HMA and HMB data increases the statistical precision as it allows for a larger sample size. MSAC noted that while the mechanism of action may be the same across the population, analysing the subgroup data from the BASIS and BASIS LTE studies showed variation between the two populations. For example, MSAC noted that the ADAR's forest plot comparing ABRs for treated bleeds by haemophilia type show the mean between-treatment difference for the HMA population was -3.91 (95% CI: -7.10, -0.73), which maintains a noninferiority conclusion for marstacimab versus factor prophylaxis based on treated ABR. However, MSAC noted that the upper limit of the 95% CI for the treated ABR in the HMB population does not permit a conclusion of noninferiority based on a noninferiority margin of 2.5 treated bleeds/year (mean treated ABR difference 1.35 [95% CI: -1.44, 4.13]) as patients could have an additional 4.13 treated bleeds/year. MSAC noted that the population for HMB is small and acknowledged the difficulty in interpreting the analyses from a small population. MSAC considered that whilst the BASIS trial was not powered for analysis by haemophilia type, presenting the results by haemophilia and treatment type will allow MSAC to determine whether any observed differences between marstacimab and FIX are likely to be clinically important. MSAC noted the applicant's pre-MSAC response claimed PASC had advised to include patients with HMB with and without inhibitors in MSAC application 1805. However, MSAC agreed with ESC that the applicant had misinterpreted PASC's advice to expand the requested population for concizumab (application 1805) to include patients with HMB without inhibitors as well as patients with HMB with inhibitors as being advice to present a combined clinical evaluation across these patient populations.

MSAC noted the ADAR claimed marstacimab had non-inferior effectiveness compared to emicizumab in patients with HMA. MSAC noted an indirect treatment comparison (ITC) was used to compare marstacimab (from BASIS) with emicizumab (from HAVEN 3). MSAC noted the comparison did not use a common comparator (i.e. was unanchored) and attempted to adjust for confounders across the studies, including race/ethnicity. MSAC noted that there were significant differences between the studies (baselines differences, small sample size, ABR measure, geographical and temporal differences) which contributed to uncertainty in the comparison's findings. MSAC noted the applicant's pre-MSAC response acknowledged that there were no head-to-head trials between marstacimab and emicizumab, however, claimed that the ITC was an appropriate but cautious interpretation of the results. MSAC considered that, although the reported results of the ITC appeared to support the non-inferior effectiveness claim for HMA, this was highly uncertain and ultimately unsubstantiated due to the significant limitations in the study and comparison.

MSAC noted the ADAR claimed marstacimab had superior effectiveness compared to factor prophylaxis. MSAC noted in the pooled HMA and HMB population the mean ABR was 7.85 (95% CI: 5.09, 10.61) for factor prophylaxis and 5.08 (95% CI: 3.40, 6.77) for marstacimab. MSAC noted a key concern from ESC was whether using mean ABR was the appropriate measure, given the disproportionate distribution of patients across each of the bleed categories. MSAC noted the separate analysis of effectiveness outcomes by haemophilia type. MSAC noted the results presented in the ADAR indicated marstacimab had superior effectiveness over factor prophylaxis in the HMA population, but that superior effectiveness of marstacimab over factor prophylaxis in the HMB population was not supported. However, MSAC reiterated that the applicability issues of the BASIS study to the Australian population, created significant uncertainty in the results and likely overestimate the incremental effectiveness of marstacimab. As such, MSAC concluded that the claim that marstacimab had superior effectiveness compared to factor prophylaxis in the HMA population could not be substantiated.

MSAC noted that the ADAR had not included comparison against near market comparators that had recently been considered and supported by MSAC (etranacogene dezaparvovec [ED][5]) or were also currently being considered by MSAC (concizumab[6]). MSAC noted the commentary presented a preliminary assessment, which compared marstacimab with ED (MSAC application 1728.1). MSAC noted that following infusion of ED, 63% of participants reported no bleeding episodes in months 7 to 18, and 94% of participants were able to cease regular FIX prophylaxis. MSAC noted that this corresponds to a lower adjusted annualised bleeding rate (ABR) (total bleeds) than the rate of treated bleeds reported in BASIS for marstacimab. MSAC considered that the results suggested marstacimab may be inferior to ED. However, MSAC agreed with ESC that these data are highly uncertain given the naive comparison of two different outcome measures (ABR in the HOPE-B trial compared with treated bleeds in the BASIS trial). MSAC agreed with PASC advice that concizumab and ED should have been included as near-market comparators for marstacimab, noting both concizumab and ED were for treatment of patients with HMB with and without inhibitors. MSAC noted in the pre-MSAC response, that while the applicant acknowledged ED as a relevant near market comparator, they did not agree that it was an appropriate economic comparator for marstacimab. The applicant also stated that it was not public information (at the time of ADAR development for MSAC 1806) that the population of MSAC Application 1805, for concizumab, include the non-inhibitor HMB population. MSAC noted the published PICO confirmation for MSAC Application 1805 captured PASC advice that MSAC application 1805 should be expanded to include patients with HMB with and without inhibitors. MSAC noted that, while MSAC had supported ED and was currently considering concizumab, both therapies are not yet publicly funded within Australia. However, MSAC considered that a comparative assessment of effectiveness and safety of ED and concizumab (compared to marstacimab) should be included in any future submission.

MSAC noted that for the economic evaluations, the ADAR presented a cost minimisation approach (CMA) for patients with HMA against emicizumab, and a cost-utility analysis (CUA) for a pooled HMA and HMB population with factor prophylaxis as the comparator. MSAC noted that the commentary also presented a CMA for the HMB population against EHL FIX. MSAC noted that a range of alternative treatments exist for haemophilia and agreed with ESC's recommendations for a conservative approach to pricing of marstacimab, and that uncertainty in clinical benefit should be reflected through a lower acceptable cost-neutral price.

Regarding the ADAR's CMA for patients with HMA against emicizumab, MSAC noted ESC requested the model inputs be respecified to address inputs used in the ADAR which favoured marstacimab over emicizumab. MSAC noted the post-ESC respecified model included the in-confidence emicizumab price. Using the respecified model inputs, MSAC noted for marstacimab to remain cost-neutral with emicizumab over two years, the price per unit (pen) of marstacimab would need to be $redacted, which represents a redacted% price reduction from the requested price of $redacted.

Regarding the commentary's CMA for the HMB population against EHL FIX, MSAC noted that ESC had also requested the model inputs be respecified to align with the CMA for HMA and to align with previous MSAC advice for the effective price of EHL FIX. Using the post-ESC respecified model, MSAC noted for marstacimab to remain cost-neutral with EHLFIX over two years, the price

[5] MSAC application 1728.1 - Etranacogene dezaparvovec for the treatment of haemophilia B, considered and supported by MSAC at its July 2025 meeting. https://www.msac.gov.au/applications/1728-1

[6] MSAC application 1805 - Concizumab for routine prophylaxis to prevent bleeding in patients with haemophilia B, scheduled for consideration by MSAC at its April 2026 meeting. https://www.msac.gov.au/applications/1805

per unit (pen) of marstacimab would need to be $**redacted**, which represents a **redacted**% price reduction from the requested price of $**redacted**.

MSAC noted the applicant's pre-MSAC response did not agree with the re-specified input around dose escalation (13.9% suggested by ESC). The applicant stated that the analyses should be consistent with that observed in the BASIS study. The applicant stated that this would be 4.7% in year 1, and 12.3% in Year 2, derived from the average dose administered in the BASIS LTE study. The applicant also disagreed with the respecified input for the average dose of EHL FIX. The applicant argued that average dose of EHL FIX should be based on ABDR data reflecting actual utilisation in the Australian setting in the population of interest. However, MSAC noted a major limitation of the ABDR data is that it is not specific to a particular FIX product. MSAC agreed with ESC's advice that the average dose should align with the TGA recommended PI dose for the relevant EHL FIX product. In addition, the applicant disagreed with ESC's advice to derive the nurse administration cost from the National Efficient Price Determination (NEPD) 2025-26. The applicant stated the PBAC Manual of Resource Items and their Associated Unit Costs for costing non-admitted services, provides guidance to use National Hospital Cost Data Collection (NHCDC). However, MSAC reiterated ESC advice that in the context of the current consideration it would be more appropriate to use the agreed NHCDC Tier 2 service code but apply the weighted price from the NEPD as this represents the national benchmark of efficient costs and is a more recent source (2025-2026) than the NHCDC weights (2022-2023).

MSAC noted that the CUA for marstacimab versus factor prophylaxis for the pooled HMA and HMB population resulted in an incremental cost effectiveness ratio (ICER) of $**redacted** per additional quality-adjusted life year (QALY) gained over a lifetime. MSAC noted the applicant's pre-MSAC response defended the use of a CUA and reiterated their view that the mechanism of action is the same across both populations and the combination of HMA and HMB populations in the result is appropriate. MSAC appreciated that HMB is a rare disease and sample size is likely to be limited. However, MSAC agreed with PASC advice that the economic evaluations for the HMA and HMB populations would need to be separated given that each population has different primary comparators, and that if superiority cannot be demonstrated for the comparison of marstacimab versus EHL FIX prophylaxis, then a CMA would be the most appropriate economic evaluation for the HMB population. Therefore, MSAC agreed with ESC and considered that a CUA was not appropriate, as superiority of marstacimab versus FIX prophylaxis in the HMB population had not been established. MSAC also considered that the main comparator for the HMA population is emicizumab, not FVIII prophylaxis.

After review, MSAC concluded that the economic evaluations for marstacimab could not be used to establish the cost-effectiveness of marstacimab due to the significant uncertainty in the evidence base of the application. MSAC also noted the lack of established cost-effectiveness for currently funded haemophilia therapies, including bypassing agents 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). MSAC noted the post-ESC respecified financial analysis was performed using the respecified inputs from the economic evaluation, including the resultant cost-neutral prices for marstacimab. The in-confidence effective prices for emicizumab, EHL FVIII and EHL FIX were also used. MSAC noted the respecified financial analyses showed that if marstacimab was listed for HMA and HMB, the net impact to the health care system would be $**redacted** in year 1. This would increase to a peak of $**redacted** in year 3, before decreasing to -$**redacted** in year 6. MSAC noted this resulted in a revised weighted average price of marstacimab (for both HMA and HMB) of $**redacted**, a **redacted**% reduction from that proposed in the ADAR. MSAC noted that there is a strong patient

preference for subcutaneous administration and considered that this may lead to higher uptake than predicted.

MSAC noted that the pre-MSAC response agreed with most of the financial issues identified by ESC, however, did not accept the advice from ESC for dose escalation. MSAC noted the applicant provided revised estimates. MSAC acknowledged that the applicant did not have visibility on the price of emicizumab so could not make all requested revisions. MSAC noted that, using the pre-MSAC responses analysis, it would result in net costs to the NBA of about $**redacted** in year 1 to $**redacted** in year 6.

MSAC noted the pre-MSAC response agreed with ESC that a risk-sharing arrangement would be unsuitable. MSAC considered that there is insufficient evidence for MSAC to provide advice on the parameters of a funding arrangement.

Overall, MSAC did not support listing of marstacimab to treat people aged 12 years or over with severe HMA or HMB, without inhibitors. MSAC considered that the clinical claims of safety and effectiveness of marstacimab versus emicizumab and factor prophylaxis could not be substantiated. MSAC considered that the uncertainty in the clinical evidence flowed through to the economic evaluations, and therefore the cost-effectiveness of marstacimab could not be reliably established. MSAC also considered that despite overall net financial cost being low, there was high financial risk from uncertainties regarding uptake and cost.

MSAC advised that any resubmission for marstacimab would require evidence that demonstrates the comparative safety and effectiveness of marstacimab, in both or either HMA/HMB populations, and that is generalisable to the Australian clinical setting. The resubmission should also:

- Present the results of the BASIS trial by haemophilia and treatment type, to allow a determination of whether any observed differences between marstacimab and FIX are likely to be clinically important.
- Provide further comparative evidence, including comparison to near-market comparators.
- Align the economic and financial analysis with ESC and MSAC advice.

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.

4. Background

MSAC has not previously considered marstacimab for routine prophylaxis to prevent bleeding in patients with haemophilia.

MSAC has previously considered NPPL listing of another monoclonal antibody treatment for prophylactic treatment of haemophilia (without inhibitors). In August 2019 MSAC considered listing emicizumab for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with moderate to severe HMA who did not have Factor VIII inhibitors (MSAC 1579). At the same meeting, MSAC also considered a resubmission of emicizumab for patients who had Factor VIII inhibitors (MSAC 1510.1). The resubmission included a reduced price-point that was weighted across all haemophilia A patients (with and without inhibitors).

MSAC supported the funding of emicizumab for patients with HMA with and without inhibitors but advised that the final price was subject to negotiation and financial risk share arrangement.

Table 1 Summary of key matters of concern from MSAC Application 1579

Component	Matters of concern in MSAC Application 1579	How MSAC application 1806 addresses the similar issue
Requested population	ESC noted that there was potential for leakage from the relatively small population of moderate–severe HMA patients to the relatively large population of mild HMA, given the broader TGA-approved indication. *PSD MSAC 1579, p.17*	The population requested in the ADAR aligns with the current TGA-approved indications.
Economics	MSAC advised that the shadow price for emicizumab should be linked to its ability to reduce annualised bleed rates, in patient who were previously receiving factor prophylaxis, noting the consequences of bleeds for patient outcomes and extra costs. *PSD MSAC 1579, p.4*	For HMA and HMB, an additional clinically meaningful reduction in annualised bleeding rates from treatment with marstacimab, rather than factor prophylaxis, is optimistic as most patients received SHL prophylaxis in the key trial. This does not reflect current Australian clinical practice, where the majority of patients receive EHL prophylaxis. For HMA, the claim that marstacimab is non-inferior compared to emicizumab is based on an indirect treatment comparison; leading to uncertainty about whether bleeding outcomes between these treatments are similar.

ADAR = applicant developed assessment report; ESC = evaluation sub-committee; HMA = haemophilia A; MSAC = Medical Services Advisory Committee; PSD = public summary document; TGA = Therapeutic Goods Administration

5. Prerequisites to implementation of any funding advice

Marstacimab is listed on the Australian Register of Therapeutic Goods (AUST R 438990 listing effective 29 January 2025) and indicated for the routine prophylaxis of bleeding episodes in patients 12 years of age and older with:

- severe HMA (congenital Factor VIII [FVIII] deficiency, FVIII <1% activity) without FVIII inhibitors, or;
- severe HMB (congenital Factor IX [FIX] deficiency, FIX <1% activity) without FIX inhibitors

Currently, based on the Australian Product Information[7] for marstacimab, there are no requirements for monitoring for the presence of FVIII/FIX inhibitors during treatment with marstacimab.

6. Proposal for public funding

Marstacimab is a human monoclonal antibody (immunoglobulin G isotype, subclass 1 [IgG1]). Marstacimab is delivered prophylactically as a once-weekly subcutaneous injection using a pen device, which may be self-administered, or by a parent or guardian for younger children. The

[7]TGA 2025. Australian Product Information for marstacimab.

dosing regimen and frequency is the same, regardless of whether the individual has HMA or HMB.

In the human body, blood coagulation is achieved via a highly regulated cascade of plasma proteins. The coagulation cascade is activated upon injury to stop bleeding and shut down when bleeding has stopped to prevent thrombosis. Regulation is achieved by two overlapping pathways: the extrinsic (initiation) pathway and the intrinsic (amplification) pathway. In haemophilia, individuals retain some ability to control bleeding via the extrinsic pathway. However, this is not sufficient to control major or spontaneous bleeds as this pathway is shut down by the tissue factor pathway inhibitor (TFPI). TFPI is an inhibitor of the clotting cascade. Marstacimab binds and inhibits TFPI, thereby enhancing the extrinsic pathway, and bypassing the requirement to replace FVIII or FIX.

The application claimed that marstacimab is expected to reduce the frequency of bleeds and prevent the chronic pain and joint damage associated with haemophilia in the longer term.

The ADAR sought listing of marstacimab on the NPPL for routine prophylaxis to prevent bleeding in patients with severe Haemophilia (HMA and HMB) without inhibitors.

7. Population

Patients proposed to be eligible for treatment with marstacimab include children and adults aged 12 years and over, with severe HMA (congenital FVIII deficiency, FVIII < 1%) or severe HMB (congenital FIX deficiency, FIX <1%) without inhibitors to FVIII or FIX, respectively. This population aligns with the registered indication for marstacimab listed in the Australian Register of Therapeutic Goods (ARTG) in 2025 (ID 438990).

Haemophilia is an X-linked congenital bleeding disorder, caused by a deficiency in coagulation FVIII in HMA or coagulation FIX in HMB. This deficiency arises from the variants in the *F8* or *F9* genes, which encode the respective clotting factors. The clotting cascade involves a complex interaction of the coagulation factors. In HMA and HMB, the disruption of FVIII and FIX impairs the cascade, resulting in prolonged bleeding.

There are three levels of haemophilia: mild, moderate and severe. The level of severity depends on the amount of relative clotting factor activity in the person's blood compared to normal. Severe haemophilia has an activity of <1% relative to normal and is typically identified early in life. Individuals with severe haemophilia experience bleeds from trauma, or bleeding may occur spontaneously. Spontaneous bleeds often occur in joints and can lead to pain and swelling. If this occurs repeatedly in the same joint, this is called a "target joint bleed" and can result in permanent damage, leading to arthritis, chronic pain, and loss of joint function (Haemophilia Foundation Australia, 2023)[8].

The current standard of care for people with severe HMA involves either prophylactic subcutaneous injections of emicizumab (administered 1-4 times per month) or prophylactic infusions of FVIII concentrate (administered 1-2 times per week for extended half-life (EHL) products). Patients receiving prophylactic treatment with either emicizumab or FVIII replacement may still require on-demand FVIII replacement, such as for managing breakthrough bleeding episodes or as surgical cover (prophylaxis) prior to surgical procedures.

[8] Haemophilia Foundation Australia 2023. Haemophilia. Darling. VIC: HFA.

It was reported that 356/561 (63.5%) patients aged 12 years and older with severe HMA in Australia were on a prophylactic regimen of FVIII at some point in 2021-2022 (National Blood Authority 2023a)[9] although it is likely that at least some of these swapped to prophylaxis with emicizumab (given the sum of those who received emicizumab and prophylactic FVIII summed to more than 100%). National Blood Authority usage estimates for 2021-2022 report that: 59.5% of individuals with severe HMA use an EHL product; 38.5% use an SHL product; and 2% were using a plasma-derived FVIII product (National Blood Authority 2023b)[10].

The current standard of care for people with severe HMB involves prophylactic infusions of EHL FIX concentrate (administered once per 2-3 weeks). In addition, FIX concentrate is also used on-demand to manage breakthrough bleeds or as cover prior to surgical procedures.

Among the Australian HMB population, the majority (80%) use an EHL product rather than an SHL product (National Blood Authority 2023a).

Patients with HMA or HMB receiving factor prophylaxis are typically screened for inhibitor development if they exhibit an unexpected clinical response, have undergone intensive factor treatment, or are scheduled for surgical procedures. If high inhibitor titres are detected, immune tolerance induction (ITI) with factor replacement is initiated, alongside on-demand use of by-passing agents (BPAs) as needed. If ITI fails, subsequent treatment options include on-demand or prophylactic BPAs, or (for patients with HMA) prophylactic emicizumab in combination with a BPA.

In Australia, approximately one in 6,000 males has HMA and one in 25,000-30,000 males has HMB, resulting in over 3,000 individuals currently diagnosed across the two conditions. The Australian Bleeding Disorders Registry (ABDR) registered 561 severe HMA cases and 90 severe HMB cases in people aged 12 years or over in 2021-22, and these people may potentially receive marstacimab if they do not have active inhibitors.

8. Comparator

The primary comparator for people with HMA is emicizumab, which is a bispecific, humanised monoclonal antibody. The treatment brings together activated Factor IX and Factor X in the clotting cascade, thereby replacing FVIII. The secondary comparator is EHL FVIII replacement prophylaxis via intravenous infusion.

The primary comparator for people with HMB is EHL FIX replacement prophylaxis via intravenous infusion. However, in July 2025 MSAC supported public funding for etranacogene dezaparvovec (ED; also known as Hemgenix®) for adults with moderately severe or severe HMB (MSAC 1728.1 PSD). PASC considered that ED is a near market comparator to marstacimab.

These comparators are based on the ratified PICO Confirmation for this application, wherein PASC advised:

"... EHL factor replacement products are only marginally superior to SHL products in regard to bleeding rates, but are associated with improved convenience due to reduced dosing frequency (which may improve quality of life). PASC noted that although there are SHL factor replacement products available on the NPPL, the vast majority of patients receiving factor replacement are on

[9] National Blood Authority 2023a. 'Analyses requested by Pfizer from the ABDR', NBA.

[10] National Blood Authority 2023b. Australian Blood Disorders Registry Annual Report 2021-22, *NBA.*

EHL products, and the clinical expert also advised that SHL is rarely used now. Therefore, SHL was considered to not be a valid comparator."

In the ratified PICO, PASC further noted:

"... concizumab has been registered on the ARTG for patients at least 12 years of age who have HMA or HMB. PASC noted that an application for concizumab has been submitted for consideration by MSAC for patients with HMB with Factor IX inhibitors. PASC noted this was not the same targeted population as marstacimab and did not consider that concizumab was a relevant near-market comparator. However, if the proposal for public funding of concizumab is expanded to include patients with HMA or HMB without inhibitors, it would be a relevant near-market comparator against marstacimab for the HMA and HMB patient populations proposed in the current application."

The applicant for MSAC 1805 (concizumab) has since expanded the population to include patients with HMB without inhibitors. Therefore, concizumab may be considered another a near market comparator.

9. Summary of public consultation input

Consultation input was welcomed from:

1806 – Marstacimab for routine prophylaxis to prevent bleeding in patients with haemophilia	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
Health Professionals (1)	
I am a health professional or health academic working in the area.	1
Grand Total	**6**

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 marstacimab for routine prophylaxis to prevent bleeding in patients with haemophilia.

Comments on PICO

Consultation input from HFA and AHCDO states that the application narrowly defines the eligible population, excluding patients with moderate haemophilia. AHCDO proposed that the population

be expanded to include people with moderate haemophilia without inhibitors, where a severe bleeding phenotype is present, as they will also be candidates for prophylaxis. HFA also suggested that MSAC give consideration to including this population. AHCDO also included people with moderate haemophilia A and B where the individual is already receiving prophylaxis with an intravenous factor concentrate.

The consultation input broadly agreed with the proposed comparators. However, AHCDO noted that the proportion of severe haemophilia A patients on emicizumab is likely to be higher than outlined in the 2023 Annual Report.

Perceived Advantages

Consultation input viewed the route and ease of administration of marstacimab as a major advantage. HFA noted that people administer marstacimab once weekly by subcutaneous injection, using a pen device. This mode of administration has many benefits for people with haemophilia:

- a weekly subcutaneous injection with a pen device is much easier to manage than slow infusion into a vein and will not impact on veins
- it does not require extra equipment such as tourniquets and to create a sterile environment
- while the product needs to be refrigerated, it is self-contained and inconspicuous – easier to travel with and not misunderstood as illicit drug use
- hand dexterity is not required so it is easy for people with arthritis or shaky hands or less skilled carers to administer
- the administration with a fixed dose supports treatment regimen adherence.

HFA noted the burden with intravenous infusions is considerable and provided the results of surveys conducted with people with haemophilia and their carers, which demonstrated a preference for easier and less painful administration of treatment options.

AHCDO noted that funding of marstacimab would facilitate eligible people with haemophilia B still receiving therapy on demand to move to prophylaxis (achieving standard of care). They also noted that marstacimab would be a more feasible option for effective prophylaxis in patients having difficulty with weekly intravenous access or who are unable to comply with frequent intravenous infusions. They also noted that effective prophylaxis would limit breakthrough bleeds and improve long term joint health and functioning.

All consultation input stated that access to a subcutaneous prophylactic treatment for people with severe haemophilia who cannot receive emicizumab would be considered an improvement. They noted overall, it would reduce the burden of care, reduce symptoms, allow individuals to participate in more activities, and improve quality of life. They stated it may also help treatment compliance in adolescents and young adults.

Perceived Disadvantages

AHCDO noted that for patients in the BASIS trial where long term follow up data was available, the annualised bleeding rate (ABR) for patients on marstacimab (2.3) was higher than many would consider acceptable in the era of “aiming for zero bleeds.” They note that haemophilia A populations on emicizumab have a high percentage of zero bleeds and state the ABR is typically <1. However, AHCDO noted that for eligible people with haemophilia B, funding of marstacimab would represent the first subcutaneous option for prophylaxis, which they consider an improvement in treatment options for this group.

Support for Implementation and Issues

Consultation input was supportive of implementation of funding for marstacimab, and respondents did not see any barriers to implementation. AHCDO noted that the pen device administration makes marstacimab a straightforward treatment to implement and will reduce reliance on consumables and outpatient haemophilia treatment centre services. HFA expressed concerns that limiting home administration to 'self-administration by the patient or parent/guardian for younger children' fails to consider individual situations. They recommend changing this requirement to 'self-administration by the patient, parent/guardian or other suitable carer' asserting that this would better account for environments such as nursing homes and carers who are partners, friends or other people involved in the care of the adult or child with haemophilia.

THANZ and AHCDO both noted that the Australian Bleeding Disorders Registry (ABDR) will capture data to monitor the use/effectiveness of marstacimab. Patients can record the number of bleeds in myABDR. AHCDO noted that it will be very important to closely monitor the long term follow up data to ensure that safety is maintained with regard to thromboembolic events.

PPA noted that marstacimab targets the tissue factor pathway in ways that cannot currently be monitored. Should monitoring of Tissue Factor Pathway Inhibitor (TFPI) inhibitors become required, new assays may need to be set up.

AHCDO advised that marstacimab does not eliminate the need for factor inhibitor testing, as factor replacement may be required for breakthrough bleeds and surgical prophylaxis.

10. Characteristics of the evidence base

Characteristics of the evidence base are summarised in Table 2.

The BASIS trial and BASIS LTE provided direct data for the analysis of marstacimab versus FVIII and FIX prophylaxis, relevant to the HMA and HMB populations, respectively.

Given that no head-to-head trials were identified comparing marstacimab and emicizumab, the ADAR used an indirect treatment comparison (ITC), in which adjusted analyses compared efficacy outcomes for patients treated with marstacimab in the BASIS trial with patients who received emicizumab in Group D of the HAVEN 3 study. The limitations of these data are discussed in the context of the results reported for the HMA population in Section 8 (Comparative safety) and Section 9 (Comparative effectiveness).

Table 2 Key features of the included evidence

References	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Marstacimab versus FVIII prophylaxis (EHL/SHL not defined)						
BASIS	65	Before and after case series (one-way cross-over); 6-month OP during which participants received FVIII and 12-month ATP in which participants crossed over to marstacimab	*Moderate risk of bias (non-randomised, open-label, with low generalisability to Australian context)*	Severe HMA, no inhibitors PPX	ABR, joint bleeds, target joint bleeds, HJHS, HRQoL, total factor/ bypass consumption, AEs, SAEs, immunogenicity (ADAs and NAbs)	Yes; see Section 11 (Economic evaluation)
BASIS LTE	65	Extension study of above; additional 16 months of follow-up at the time of the interim CSR, and 18.9 months of additional follow-up at the time of the ISTH Congress in June 2025				
Emicizumab versus no prophylaxis						
HAVEN 3 (Group D)	63	Before and after case series (one-way cross-over)	*Not stated*	Severe HMA, no inhibitors PPX	ABR, joint bleeds, AEs, SAEs	-
Marstacimab versus FIX prophylaxis (EHL/SHL not defined)						
BASIS	18	Before and after case series (one-way cross-over); 6-month OP during which participants received FIX and 12-month ATP in which participants crossed over to marstacimab	*Moderate risk of bias (non-randomised, open-label, with low generalisability to Australian context)*	Severe or moderately severe HMB, no inhibitors PPX (one patient enrolled with moderately severe HMB; not included in outcomes analysis)	ABR, joint bleeds, target joint bleeds, HJHS, HRQoL, total factor/ bypass consumption, AEs, SAEs, immunogenicity (ADAs and NAbs)	Yes; see Section 11 (Economic evaluation)
BASIS LTE	18	Extension study of above; additional 16 months of follow-up at the time of the interim CSR, and 18.9 months of additional follow-up at the time of the ISTH Congress in June 2025				

ABR = annualised bleeding rate; ADA = anti-drug antibodies; AE = adverse events; ATP = active treatment phase; CSR = clinical study report; DB = double blind; EHL = Extended half-life; HJHS = Haemophilia Joint Health Score; HRQoL = health-related quality of life; HMA = haemophilia A; HMB = haemophilia B; ISTH = International Society on Thrombosis and Haemostasis; NAbs = neutralising antibodies; OL = open label; OnD = On-demand; OP = observational phase; PPX = prophylaxis; SAE = serious adverse events (specifically: thrombotic events, severe hypersensitivity, and anaphylactic reactions); SHL = standard half-life

11. Comparative safety

Haemophilia A

Marstacimab versus emicizumab

The ADAR provided a side-by-side qualitative comparison of safety endpoints for marstacimab and emicizumab, stating that an ITC of safety outcomes for marstacimab versus emicizumab was inappropriate due to the level of heterogeneity between BASIS and HAVEN 3 for the assessment methods, timing and reporting of safety outcomes.

Based on a side-by-side comparison of safety endpoints between the BASIS (marstacimab) and HAVEN 3 (emicizumab) trials, no substantive differences in safety outcomes between treated patients were observed (Table 3). Group D refers to the group in HAVEN 3 receiving prophylaxis with emicizumab. The number of serious adverse events (SAEs), treatment-related SAEs and discontinuations due to adverse events (AEs) were similar between trials.

Findings should be interpreted cautiously due to the heterogeneity in assessment methods used in the BASIS and HAVEN 3 trials, as well as differences in the timing and reporting of safety outcomes. Median treatment exposure also differed between the trials. In HAVEN 3, patients were exposed to emicizumab treatment for 33 weeks, while in the BASIS trial, exposure to marstacimab was for 52 weeks.

Table 3 Side-by-side comparison of the safety of emicizumab and marstacimab

Variable	HAVEN 3 Group D (emicizumab) N=63	BASIS ATP Non-inhibitor population with prophylaxis at OP (marstacimab) N=83
Median duration of exposure, weeks (range)	33.1 (18.0, 48.1)	52.0 (4.0, 56.0)
AEs, n	236	262
Participants with AEs, n (%)	NR	62 (74.7)
Injection site reaction	20 (31.7)	9 (10.8)
Upper respiratory infection	8 (12.7)	1 (1.2)
Nasopharyngitis	10 (15.9)	0
Arthralgia	14 (22.2)	3 (3.6)
Headache	5 (7.9)	6 (7.2)
COVID-19	NR	18 (21.7)
Contusion	NR	5 (6.0)
Dental caries	NR	4 (4.8)
Pruritis	NR	2 (2.4)
SAEs, n	10	8
Participants with SAEs, n (%)	NR	7 (8.4)
Participants with tx-related SAEs, n (%)	0	1 (1.2)
Participants with AEs leading to tx discontinuation, n (%)	0	1 (1.2)

Source: ADAR 1806 Table 38
AE = adverse events; ATP = active treatment phase; NR = not reported; OP = observational phase; SAEs = serious adverse events; tx = treatment

Marstacimab versus EHL FVIII prophylaxis

The safety analysis of marstacimab vs EHL FVIII prophylaxis was not evaluable due to the pooling of data for HMA and HMB.

Haemophilia B

Marstacimab versus EHL FIX prophylaxis

The safety analysis of marstacimab vs EHL FIX prophylaxis was not evaluable due to the pooling of data for HMA and HMB.

Haemophilia A and B combined

The pooled adverse events observed for HMA and HMB, occurring during the factor prophylaxis and active marstacimab treatment phases in the BASIS trial, are given in Table 4.

Table 4 Summary of all-cause AEs in BASIS trial, pooled for HMA and HMB non-inhibitor cohort, by age group, All Safety Set

	Adults (18 to <75 yrs)		Adolescents (12 to <18 yrs)		All	
n[1]	OP (factor prophylaxis) N=73	ATP (marstacimab) N=66	OP (factor prophylaxis) N=18	ATP (marstacimab) N=17	OP (factor prophylaxis) N=91	ATP (marstacimab) N=83
Total AEs	33	226	11	36	44	262
AEs	18 (24.7)	52 (78.8)	7 (38.9)	14 (82.4)	25 (27.5)	62 (74.7)
Medication errors	0	3 (4.5)	0	2 (11.8)	0	5 (6.0)
SAEs	1 (1.4)	6 (9.1)	1 (5.6)	1 (5.9)	1 (2.2)	7 (8.4)
Grade 3 AEs	1 (1.4)	5 (7.6)	0	1 (5.9)	1 (1.1)	6 (7.2)
Grade 4+ AEs	0	0	0	0	0	0
AEs leading to discontinuation of study phase	0	1 (1.5)	0	0	0	1 (1.2)
AEs leading to dose reduction or temporary discontinuation	0	12 (18.2)	0	2 (11.8)	0	14 (16.9)

Source: ADAR 1806 Table 33

AE = adverse event; ATP = active treatment phase; HMA = haemophilia A; HMB = haemophilia B; OP = observational phase; SAE = serious adverse event

[1] n = number of participants with event except for Total AEs

The majority of treatment emergent adverse events (TEAEs) in the active treatment phase (ATP) of the BASIS trial (during which participants crossed over to marstacimab from the observational phase (OP) on prior prophylaxis), were injection site pruritis (4 [4.8%] participants), injection site erythema (3 [3.6%] participants), and prothrombin fragment 1.2 increased (3 [3.6%] participants). All events were mild-moderate in severity.

There were no deaths, and no serious adverse events (SAEs) related to thromboembolism in the HMA and HMB non-inhibitor cohort of the BASIS trial. One SAE was related to the treatment: one

incident of Grade 1 peripheral swelling (calf swelling) occurred during the ATP. Five (6.0%) medication errors were reported during the ATP.

There were no dose reductions due to AEs during the OP or ATP.

Based on the adverse event data combined for HMA and HMB, the applicant concluded that marstacimab has non-inferior safety relative to FVIII prophylaxis for HMA and non-inferior safety relative to FIX for HMB. These combined data are inappropriate to support the claims of non-inferior safety, which have been made for HMA and HMB separately in the absence of safety data specific to these subgroups. PASC advised that the results for HMA and HMB would need to be presented separately for the purposes of the health technology assessment. PASC noted that whilst the BASIS trial was not powered for analysis by haemophilia type, presenting the results by haemophilia type will allow the committees (ESC and MSAC) to determine whether any observed differences are likely to be clinically important (even if underpowered for statistical comparisons).

The frequency of AEs and SAEs combined for HMA and HMB do not appear to be comparable between the OP of the BASIS trial (during which patients received factor prophylaxis) and the ATP of the BASIS trial (during which patients received marstacimab), even taking into account differences in the duration of exposure to factor prophylaxis (6 months) and marstacimab (12 months).

Differences in prophylactic treatment relevant to the study population compared to contemporary Australian clinical practice where prophylaxis with an EHL rather than an SHL product is standard are unlikely to contribute to the differences observed. MSAC has previously noted (MSAC 1511 PSD) that the safety of EHL products is similar to that of SHL products. The rate of serious adverse events after receiving EHL products appears to be low (<1%). MSAC noted that EHL products appear to be no more likely than SHL products to result in the development of inhibitors.

The ADAR confirmed the applicant's pre-assessment advice to PASC that anti-drug antibodies (ADAs) developed in 19.8% of evaluable patients (23/116). Most instances of ADAs (61%, 14/23) were judged to be transient (defined as positivity for <16 weeks). By the end of the ATP study period, 95.7% (22/23) had resolved. Neutralising antibodies (nAb) developed in 5.2% of the study cohort (6/116). All were transient and resolved by the end of the ATP study period.

At pre-assessment, it was also stated that management of ADAs would be left up to the treating clinician's judgement. The Food and Drug Administration (FDA) prescribing information for marstacimab does not recommend any clinical course of management, stating "There was no identified clinically significant effect of ADAs, including nAbs, on safety or efficacy of marstacimab" over 12 months treatment duration. The applicant stated that similar wording has been included in the proposed TGA product information for marstacimab.

PASC noted from the applicant's clinical expert that there is no strong justification from the available evidence for the need for regular ADA testing and that this testing, if performed, should be driven by clinical requirements.

PASC considered that routine monitoring of ADAs would not be required as data provided showed a very low incidence of these, and they tend not to influence the efficacy of marstacimab. PASC recommended that the assessment report include the information on ADAs collected in the BASIS trial, but further information would not be required on this outcome.

The ADAR narratively summarised AEs that occurred with dose escalation in the BASIS trial. The ADAR reported that among the 14 participants with dose escalation from 150 mg to 300 mg marstacimab during the ATP, none experienced an SAE or TEAE that led to discontinuation of treatment (mean exposure of 118.6 days (SD: 56.26)) days while on 300 mg marstacimab.

One participant had a treatment-related TEAE (Grade 1 arthralgia at Day 190) while on the higher dose; four other participants reported TEAEs after dose escalation (Grade 1 joint range of motion reduction, Grade 2 laryngitis, Grade 2 arthralgia, Grade 1 rhinitis), two participants who had their dose escalated did not experience any TEAEs throughout the study and all others had non-treatment-related TEAEs during the 150 mg dosing regimen.

For the BASIS LTE, the ADAR reported that 29% of participants (n=25) had a TEAE at the time of interim analysis (10 March 2023). Most of these events (84%) were mild (Grade 1 severity) and the most commonly recorded event was nasopharyngitis (n=4 participants, 4.6%). COVID-19 and injection site reaction were the other common TEAEs, which were reported in 3 participants (3.4%) each (BASIS LTE interim CSR p53). TEAE frequency was similar across age subgroups (adolescents 12 to <18 years vs. adults 18 to <75 years). There were no unanticipated risks in either age group. Four participants (29%) in the adolescent group and 21 participants (29%) in the adult group reported an AE (BASIS LTE interim CSR p58). Treatment-related AEs were uncommon (n=3 participants). The only reported treatment-related AEs were 4 events of injection site reaction (n=3 participants, 3.4%). Three events were Grade 1 (n=2 participants, 2.3%) and one event was Grade 2 (n=1 participant, 1.1%) (BASIS LTE interim CSR p58).

Four participants underwent dose escalation from 150 mg to 300 mg during the interim analysis period of the BASIS LTE (10 participants had had their dose previously escalated to 300 mg in the main BASIS study and this was continued in the BASIS LTE). Mean exposure was 149.3±125.9 days on 300 mg marstacimab (BASIS LTE interim CSR p59).

During the BASIS LTE, the 14 participants with marstacimab dosing of 300 mg reported TEAEs as follows:

- 1 participant reported 1 treatment-related AE of injection site reaction (Grade 1; mild severity)
- 2 participants reported COVID-19 infection as an AE (not treatment-related)
- 1 participant reported nasopharyngitis/common cold as an AE (not treatment-related)

There were no deaths among participants during the BASIS LTE and the incidence of SAEs was low (n=2 participants, 2.3%) at the time of the interim analysis. One participant experienced a head contusion and another experienced haemarthrosis of the hip. Both SAEs resolved and the participants continued treatment with marstacimab. These events were determined not to be treatment-related (BASIS LTE interim CSR p61).

None of the AEs or SAEs resulted in permanent discontinuation of treatment, while AEs in 3 participants, led to 3 temporary discontinuations. Two were due to COVID-19 and one was due to haemarthrosis. Neither of these events were considered treatment-related. There were no dose reductions due to AEs (BASIS LTE interim CSR p62-63).

12. Comparative effectiveness

Haemophilia A

Marstacimab versus emicizumab

No head-to-head trials were identified comparing marstacimab and emicizumab. The ADAR therefore used an ITC based on a systematic literature review performed by IQVIA (2024)[11]. IQVIA

[11] IQVIA (2024). Marstacimab for the Treatment of Haemophilia A and B: A Systematic Literature Review, Feasibility Assessment, and Indirect Treatment Comparison.

determined that the HAVEN 3 study was the only study on emicizumab that provided sufficient baseline characteristics to incorporate into the ITC. Particularly, HAVEN 3 was the only trial identified to have a defined study population comparable to participants with HMA in the BASIS trial in terms of its restriction to individuals who had severe disease and no inhibitors. The ADAR noted that there were important differences between the clinical management of bleeding events between the BASIS and HAVEN 3 trials. Large differences between treatment effect modifiers and prognostic factors required the results to be adjusted to reduce bias. Methodology for adjustment varied across the different modifiers, prognostic factors and outcome measures of interest.

After adjustments, there were no significant differences between annualised bleeding rates (ABRs) in those receiving marstacimab (in the BASIS trial) and those receiving emicizumab (in the HAVEN 3 trial) (Table 5). Likewise, there were no significant differences between the proportion of patients with zero bleeding events over the 6-month follow-up periods. These data appear to support the claim of non-inferiority between marstacimab and emicizumab. However, these results are highly uncertain, as they relied on statistical adjustments, and could not fully account for geographical and temporal differences between the trials or unmeasured confounding.

These methodological limitations of the ITC were summarised in the ADAR as follows:

1. BASIS trial participants tended to have more severe disease at baseline compared to those in HAVEN 3. While restriction and population-adjustment were used to control for these differences risk of bias due to residual imbalances remain, e.g. lack of information on additional covariates that would otherwise allow a more complete adjustment of baseline differences in disease severity.
2. There were geographical and temporal differences between the HAVEN 3 and BASIS trials that could not be fully accounted for within the ITC analyses. In the BASIS trial, there were a higher proportion of non-white individuals compared to HAVEN 3, potentially due to differences in geographic distribution of participants. Differences in clinical practice across geographical locations could explain between trial heterogeneity in disease severity and in the treatment of breakthrough bleeding. Temporal differences in clinical practice may also account in part for this heterogeneity. For example, the data cut-off date for HAVEN 3 was September 2017 and enrolment for BASIS began in March 2020. The COVID-19 pandemic, which began at the end of 2019, may have had a negative impact on access to healthcare resources and the physical, psychological and socio-economic wellbeing of individuals enrolled in BASIS. Given that the ITC analyses could not fully account for such geographical and temporal differences, findings should be interpreted with caution.
3. The ITC estimates lacked precision due to limited sample sizes. The BASIS trial enrolled participants with both HMA and HMB who received prior prophylaxis or on-demand therapy. To facilitate the unanchored ITC with emicizumab, analyses were restricted to individuals with severe HMA who received prior prophylaxis. Since BASIS was not designed to detect subgroup differences based on haemophilia type and prior treatment regimen, the sample size was limited, and this resulted in wide confidence intervals reflecting statistical imprecision.

An ongoing trial (NCT06703606) is assessing the impact of patients with severe HMA switching from emicizumab to marstacimab, but this within-patient comparison is expected to only be completed in 2027.

Table 5 Results for the unanchored indirect simulated treatment comparison (STC) of marstacimab (BASIS) versus emicizumab (HAVEN 3 Group D) among individuals with severe HMA without inhibitors who received prior FVIII prophylaxis

Outcome	Trial Arm	n	Outcome[1] (95% CI)	Effect Estimate[2] (95% CI)	p-value
Main analyses: total bleeding events					
Total ABR	BASIS: naïve	65	6.18 (4.33 to 8.82)	1.87 (1.11 to 3.18)	0.02
	BASIS: STC[3]	65	3.58 (2.37 to 5.41)	1.08 (0.61 to 1.91)	0.79
	HAVEN 3	63	3.3 (2.2 to 4.8)	-	-
% with zero total bleeding events	BASIS: naïve	65	36.9 (26.1 to 49.2)	0.73 (0.36 to 1.48)	0.39
	BASIS: STC[3]	65	34.0 (19.3 to 52.5)	0.64 (0.26 to 1.60)	0.35
	HAVEN 3	63	44.4 (31.9 to 57.5)	-	-
Sensitivity analysis 1: BASIS dose-escalation					
Total ABR	BASIS: naïve	65	5.78 (4.09 to 8.17)	1.75 (1.04 to 2.95)	0.04
	BASIS: STC[3]	65	3.60 (2.40 to 5.39)	1.09 (0.62 to 1.91)	0.78
	HAVEN 3	63	3.3 (2.2 to 4.8)	-	-
Treated ABR	BASIS: naïve	65	4.88 (3.30 to 7.22)	3.05 (1.76 to 5.30)	<0.001
	BASIS: STC[3]	65	2.65 (1.70 to 4.14)	1.66 (0.92 to 3.00)	0.09
	HAVEN 3	63	1.6 (1.1 to 2.4)	-	-
Sensitivity analysis 2: treated bleeding events					
Treated ABR	BASIS: naïve	65	5.21 (3.49 to 7.77)	3.26 (1.86 to 5.69)	<0.001
	BASIS: STC	65	2.64 (1.68 to 4.15)	1.65 (0.91 to 3.00)	0.10
	HAVEN 3	63	1.6 (1.1 to 2.4)	-	-
% with zero treated bleeding events	BASIS: naïve	65	44.6 (33.1 to 56.8)	0.64 (0.32 to 1.29)	0.22
	BASIS: STC[3]	65	38.9 (22.9 to 57.6)	0.51 (0.20 to 1.26)	0.14
	HAVEN 3	63	55.6 (42.5 to 68.1)	-	-
Treated AJBR	BASIS: naïve	65	4.29 (2.76 to 6.66)	3.57 (1.80 to 7.09)	<0.001
	BASIS: STC[3]	65	1.88 (1.13 to 3.15)	1.57 (0.75 to 3.28)	0.23
	HAVEN 3	63	1.2 (0.7 to 2.0)	-	-

Source: Table 37, p. 80 ADAR 1806
ABR = annualised bleed rate; AJBR = annualised joint bleed rate; CI = confidence interval; HMA = haemophilia A; n = number of individuals; STC = simulated treatment comparison
[1] Refers to the negative binomial model-derived rate for total ABR or the percentage for zero total bleeding events
[2] Refers to the estimated rate ratio (RR) for total ABR or odds ratio (OR) for zero total bleeding events
[3] Adjusted for baseline age, prior total ABR, percent with target joints, percent Hispanic/Latino, percent White and body mass index (BMI); data for naïve comparison are unadjusted

Marstacimab versus EHL FVIII prophylaxis

Data on the annualised treated bleeding rates (treated ABR) were provided in the ADAR economic file, and used below to calculate results specific to HMA (Table 6) and HMB (Table 7).

The ADAR nominated 2.5 treated bleeds/year as the non-inferiority margin, following the methodology outlined in the FDA Guidance for Non-Inferiority Clinical Trials to Establish Effectiveness (BASIS Statistical Analysis Plan p48-52). If this is used as the minimum clinically important difference, people with HMA were more than twice as likely to have clinically important reduction in treated bleeds (n=25; 38.4%), than increase in treated bleeds (n=11; 16.9%), as a result of swapping to marstacimab from FVIII prophylaxis. A large proportion of patients would

experience no clinically important change in the number of bleeds (n=29; 44.6%). Of those receiving factor prophylaxis in the OP, 73.6% of those in the BASIS trial were receiving SHL products rather than EHL products. The ADAR claimed that the effectiveness of SHL prophylaxis was similar to EHL prophylaxis. The commentary considered this claim to be uncertain and noted that the ADAR has not presented robust evidence to support this claim.

The commentary noted from a previous MSAC application (MSAC 1511) that after patients switched to EHL prophylaxis, they had 11-83% of the bleeds they experienced while on SHL prophylaxis (MSAC 1511 PSD, p6). Australian real-world evidence also support superior outcomes associated with EHLs over SHLs (Brennan et al. 2020).[14] Therefore, the data from the BASIS trial may be more favourable to marstacimab than what would occur in the Australian setting, where the majority of patients receive EHL products.

A 2020 study by Chhabra et al[12] which analysed data from the Adelphi Disease-Specific Programmes, a health record–based survey of United States and European haematologists to estimate ABRs for patients with HMA and HMB receiving SHL versus EHL factor replacement products. The HMA analysis included 501 patients (SHL, n=435; EHL, n=66). In the combined United States/European population, mean (SD) ABR was 1.7 (1.69) for the SHL group and 1.8 (2.00) for the EHL group. The HMB analysis included 150 patients (SHL, *n*=114; EHL, *n*=36). The mean (SD) ABR in the combined United States/European population was 2.1 (2.16) for patients receiving SHL Factor IX (FIX) and 1.4 (1.48) for patients receiving EHL FIX. These data suggest that the benefit of switching from an SHL to an EHL factor replacement product, as measured by ABR reduction, may be more pronounced in the HMB population compared to the HMA population, though the data are preliminary having been based on an exploratory analysis; no tests of statistical significance nor a clear discussion of the clinical significance of the findings were provided.

Table 6 Results for estimated ABR for treated bleeds during the BASIS+BASIS LTE trial. Patients with HMA, prior prophylaxis, non-inhibitor cohort

	Factor Prophylaxis at OP	Marstacimab	Change
n	65	65	65
Treated ABR (mean ± SD)	9.16 ± 14.25	4.76 ± 7.92	-4.40 ± 13.38
Treated ABR (median [IQR])	2.14 [0.00, 5.83]	2.00 [0.0, 4.99]	0.00 [-8.98, 1.04]

ABR = annualised bleeding rate
Source: Calculated based on Economics inputs – marstacimab Attachment to ADAR 1806

Haemophilia B

Marstacimab versus EHL FIX prophylaxis

The treated ABRs for HMB were similar on average between people receiving FIX prophylaxis or marstacimab. Six people (33.3%) had clinically important reductions in the rate of bleeds that required treatment; four (22.2%) had clinically important increases in the number of bleeds that required treatment, and nine (50%) had no clinically important difference in the number of treated bleeds. The claim of the superiority of marstacimab over FIX was not substantiated. As

[12] Chhabra A, Spurden D, Fogarty PF, Tortella BJ, Rubinstein E, Harris S, Pleil AM, Mellor J, de Courcy J, Alvir J. Real-world outcomes associated with standard half-life and extended half-life factor replacement products for treatment of haemophilia A and B. Blood Coagul Fibrinolysis. 2020 Apr;31(3):186-192. doi: 10.1097/MBC.0000000000000885. PMID: 32271314; PMCID: PMC7195855. < https://pmc.ncbi.nlm.nih.gov/articles/PMC7195855/>

with HMA, most patients in the BASIS trial received SHL FIX prophylaxis rather than EHL FIX prophylaxis. This means that in Australian clinical practice, where EHL FIX is commonly used, the reduction observed in treated ABRs as a consequence of marstacimab use in BASIS/BASIS LTE, when compared to FIX prophylaxis, is unlikely to be realised.

Table 7 Results for estimated ABR for treated bleeds during the BASIS+BASIS LTE trial. Patients with HMB, prior prophylaxis, non-inhibitor cohort

	Factor Prophylaxis at OP	Marstacimab	Change
n	18	18	18
Treated ABR (mean ± SD)	3.26 ± 3.31	3.88 ± 5.09	0.62 ± 5.53
Treated ABR (median [IQR])	4.00 [0.00, 5.41]	2.00 [0.00, 5.08]	0.00 [-2.78, 0.51]

ABR = annualised bleeding rate
Source: Calculated based on Economics inputs – marstacimab Attachment to ADAR 1806

Marstacimab versus entranacogene dezaparvovec

Given MSAC supported public funding for entranocogene dezaparvovec (ED) in July 2025, ED would be a near market comparator to marstacimab in HMB. Following the infusion of ED, 63% of participants reported no bleeding episodes in months 7 to 18, and 94% of participants were able to cease regular FIX prophylaxis (Table 8). This corresponded to an adjusted ABR (*total* bleeds) of 1.51, which is lower than the rate of *treated* bleeds reported in the BASIS (marstacimab) trials. Marstacimab may therefore be inferior to ED. However, these data are highly uncertain, given the naïve comparison of two different outcome measures (ABR in HOPE-B compared to treated bleeds in the BASIS trial).

Table 8 Summary of bleeding episodes in HOPE-B study to 48 months (ED trial)

Any bleeding episode	Lead-in period (N=54)	Month 7-18	Month 7-24	Month 7-36	Month 7-48
Any episode, n (%)	40 (74.1)	20 (37.0)	27 (50.0)	31 (57.4)	32 (59.3)
Zero episodes, n (%)	14 (25.9)	34 (63.0)	27 (50.0)	23 (42.6)	22 (40.7)
Free of continuous routine prophylaxis, n (%)	0	52 (96.3)	52 (96.3)	51 (94.4)	51 (94.4)
Unadjusted ABR[a]	4.11	1.08	0.99	0.90	0.77
Adjusted ABR (95% CI)	4.19 (3.22, 5.45)	1.51 (0.81, 2.82)	1.51 (0.83, 2.76)	1.52 (0.81, 2.85)	1.63 (0.76, 3.48)
Rate ratio (95% CI)[b] p-value		**0.36 (0.20, 0.64) p=0.0002**	**0.36 (0.21, 0.63) p=0.0002**	**0.36 (0.20, 0.66) p=0.0004**	**0.39 (0.19, 0.81) p=0.0058**

Source: Table 7 of MSAC 1728.1 PSD

ABR = annualised bleeding rate; CI = confidence interval.
Note: One-sided p-value ≤ 0.025 for post-treatment / lead-in < 1 is regarded as statistically significant.
a Unadjusted ABR is calculated as ratio of total (pooled) patient number of bleeds to total (pooled) patient time of observation (in years)
b Rate ratio is calculated as post-treatment / lead-in.

Haemophilia A and B combined

The ADAR reported combined data from patients with HMA (n=65; 78.3%) and HMB (n=18; 21.7%). The ADAR combined the results of the HMA and HMB population in the analyses of all

secondary efficacy outcomes when comparing FVIII and FIX to marstacimab. Only the primary efficacy outcome of treated overall ABR was assessed for the HMA and HMB subgroups.

The economic model used the combined data, and these are therefore provided below.

Marstacimab versus factor prophylaxis

On average, the rate of treated bleeds reduced when people changed from factor concentrate to marstacimab, as shown by the primary endpoint for the BASIS trial, mean treated ABR (Table 9). However, a smaller proportion of people had no treated bleeds overall (34.9% vs 39.8%), and more people had 3 or more treated bleeds when on marstacimab rather than factor concentrate (39.8% vs 36.1%).

Table 9 Results for the ABR[a] for treated bleeds in BASIS+BASIS LTE, non-inhibitor cohort with prophylaxis at OP, mITT set[b]

	Factor Prophylaxis OP N=83	Marstacimab ATP N=83	Marstacimab LTE (interim CSR) N=58	Marstacimab LTE (ISTH 2025) N=75
Completed the phase, n (%)	83 (100)	78 (94.0)	-	-
Descriptive summary				
Mean ABR (SD)	7.88 (12.91)	5.17 (8.04)	2.12 (3.93)	-
Min, Max ABR	0.00, 59.51	0.00, 35.51	0.00, 20.39	-
0 bleeds, n (%)	33 (39.8)	29 (34.9)	36 (62.1)	-
1 bleed, n (%)	9 (10.8)	7 (8.4)	-	-
2 bleeds, n (%)	11 (13.3)	9 (10.8)	-	-
≥ 3 bleeds, n (%)	30 (36.1)	33 (39.8)	-	-
Model-based summary[c]				
Mean ABR (95% CI)	7.85 (5.09, 10.61)	5.08 (3.40, 6.77)	2.79 (1.90, 4.09)	2.79 (1.96, 3.97)
Treatment comparison: marstacimab vs factor prophylaxis[d]				
Difference estimate (95% CI)[d]	-2.77 (-5.37, -0.16)		-	-
p-value[e]	0.0376		-	-
% reduction from OP (95% CI)[f]	35.2 (5.6, 55.6)		-	-

Source: ADAR 1806, Table 24; BASIS CSR interim report body, Table 24

ABR = annualised bleeding rate; ATP = active treatment phase; CI = confidence interval; CSR = clinical study report; mITT = modified intention-to-treat; OP = observational phase; SD = standard deviation

[a] ABR refers to annualised bleeding rate calculated as the number of bleeds requiring treatment/(days on treatment period /365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.
[b] mITT set defined as participants who completed the OP and received at least 1 dose of marstacimab in the ATP. Participants who changed from the non-inhibitor cohort to the inhibitor cohort on or before ATP Day -7 testing were excluded.
[c] Based on a repeated measure negative binomial regression model via generalised estimating equation approach with identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.
[d] Non-inferiority of marstacimab prophylaxis is declared when the upper bound of the 95% CI lies below 2.5. If noninferiority is established, then a testing for superiority is to be conducted. Superiority is declared when the upper bound of the 95% CI lies below 0.
[e] p-value for the null hypothesis of difference=0.
[f] Supplemental statistics derived as (1-ratio)*100; The ratio and 95% CI were obtained from a repeated measure negative binomial regression model via generalised estimating equation approach with log link function. The working correlation was set as unstructured. The model used the number of bleeds as a response variable, treatment (marstacimab prophylaxis or routine prophylaxis) as a factor, and log time on treatment as an offset variable to account for different duration on treatment.

Factor replacement consumption

Factor consumption was included as an exploratory outcome in the ADAR and the BASIS / BASIS LTE trials (see Table 10).

For the prior factor prophylaxis group, annualised mean total factor replacement consumption was 248,871 IU during the OP and 16,246 IU during the marstacimab ATP.

At the time of the interim analysis of the BASIS LTE, the annualised mean total factor consumption was 7,529 IU in the prior prophylaxis group, consistent with a further reduction in overall factor consumption.

Table 10 Annualised factor replacement consumption during the factor prophylaxis OP and marstacimab ATP in the BASIS trial and during marstacimab treatment for the BASIS LTE (interim results)

Outcome	Factor Prophylaxis OP N=83	Marstacimab ATP N=83	Marstacimab LTE (Interim CSR) N=58	Difference (95% CI) p-value
Factor replacement consumption, total IU (annualised)	248,871	16,246	7,529	NR

Source: ADAR 1806, pp. 63, 64

Abbreviations: ATP: active treatment phase; CI: confidence interval; CSR = clinical study report; IU = international units; LTE = long-term extension; NR = not reported; OP: observational phase.

Patient reported outcomes

Patient reported outcomes (PROs) were reported as combined data for HMA and HMB. Only one included outcome measure for PROs, change in 12-month Haemo-QoL (a questionnaire used to determine self-reported QoL in adolescents) physical domain score, reached statistical significance ($p<0.05$), and no clinically important differences were observed across the other outcome measures considered (Table 11).

Table 11 Comparison of PROs for the OP and ATP of the BASIS trial

Outcome[a]	Marstacimab ATP N=63	Factor Prophylaxis OP N=63	Difference (95% CI)	p-value	Effect size
Haem-A-QoL[b] 6-month[c] PDS	-6.1 (-12.6, 0.4)	-3.0 (-8.2, 2.2)	-2.2 (-9.1, 4.6)	0.522	0.08 (negligible)
Haem-A-QoL 12-month[d] PDS	-8.3 (-15.4, -1.3)	-3.0 (-8.2, 2.2)	-5.0 (-12.4, 2.4)	0.185	-
Haem-A-QoL 6-month TS	-3.7 (-6.8, –0.6)	-1.2 (-3.5, 1.1)	-2.8 (-6.6, 1.0)	0.149	0.17 (negligible)
Haem-A-QoL 12-month TS	-4.9 (-8.1, -1.7)	-1.2 (-3.5, 1.1)	-3.7 (-8.3, 0.9)	0.111	-
Outcome	**Marstacimab ATP N=20**	**Factor Prophylaxis OP N=20**	**Difference (95% CI)**	**p-value**	**Effect size**

Haemo-QoL[f] 6-month PDS	-17.9 (-27.7, -5.4)	-0.9 (-14.3, 12.5)	-18.7 (-35.7, 5.4)	0.135	0.78 (large)
Haemo-QoL 12-month PDS	-7.9 (-28.6, -4.5)	-0.9 (-14.3, 12.5)	-14.3 (-31.2, 0.0)	0.043	-
Haemo-QoL 6-month TS	-5.0 (-10.5, 0.4)	0.8 (-6.2, 7.8)	-6.5 (-15.2, 2.2).	-	0.58 (medium)
Haemo-QoL 12-month TS	NR	NR	NR	NR	NR
Outcome	**Marstacimab ATP N=83**	**Factor Prophylaxis OP N=83**	**Difference[g] (95% CI)**	**p-value**	**Effect size**
EQ-5D-5L index score[h] 6-month	0.075 (0.018, 0.133)	0.030 (-0.014, 0.074)	0.022 (-0.043, 0.088)	0.505	0.12 (small)
EQ-5D-5L index score 12-month	0.064 (0.009, 0.119)	0.030 (-0.014, 0.074)	0.023 (-0.042, 0.087)	0.493	-
EQ-VAS score[i] 6-month	4.5 (1.4, 7.7)	3.0 (-0.6, 6.6)	0.6 (-4.0, 5.1)	0.801	0.03
EQ-VAS score 12-month	3.0 (-0.2, 6.2)	3.0 (-0.6, 6.6)	-1.5 (-6.9, 3.8)	0.578	-
PGIC-H[j] 6-month	1.8 (1.4, 2.3)	3.5 (3.0, 3.9)	-1.8 (-2.2, -1.4)	-	-
PGIC-H 12-month	NR	NR	NR	NR	NR
HAL2[k] 6-month	2.1 (-1.0, 5.1)	-0.6 (-3.0, 1.8)	2.0 (-1.8, 5.7)	NR	0.09 (negligible)
HAL2 12-month	NR	NR	NR	NR	NR
pedHAL 6-month	5.3 (-4.7, 15.3)	-1.7 (-9.8, 6.3)	6.7 (-9.3, 22.7).	NR	0.26 (small)
pedHAL[l] 12-month	NR	NR	NR	NR	NR
$HJHS_{change}$ Baseline to 6 months treatment	-0.6 (-2.2, 1.0)	1.3 (-0.7, 3.3)	-2.0 (-4.3, 0.3)	0.084	0.11 (small/negligible)

Source: BASIS CSR Tables 33 – 36; see p. 107 and p. 114 for non-tabulated results for Haemo-QoL in adolescents and PGIC-H outcomes. Several discrepancies were noted in the reported values for the between-treatment differences included from the sections of the BASIS CSR used to source these data. According to the evaluator's calculations, the point estimates are: Haem-A-QoL 6-month PDS = -3.1; Haem-A-QoL 12-month PDS = -5.3; Haem-A-QoL 6-month TS = -2.5; Haemo-QoL 12-month PDS = -7.0; Haemo-QoL 6-month TS = -5.8; EQ-5D-5L index score 6-month = 0.045; EQ-5D-5L index score 12-month = 0.034; EQ-VAS score 6-month = 1.5; EQ-VAS score 12-month = 2.7

ATP = active treatment phase; EQ-5D-5L = 5-level EQ-5D; EQ-VAS = EQ visual analogue scale; Haem-A-QoL = Haemophilia Quality of Life Questionnaire for Adults; Haemo-QoL = Haemophilia Quality of Life Questionnaire for Children and Adolescents; HAL = Haemophilia Activities List; NR = not reported; OP = observational phase; PDS = physical domain score; pedHAL = Pediatric Haemophilia Activities List; PGIC-H = Patient Global Impression of Change-Haemophilia; TS = total score

[a] All outcomes expressed as median (95% CI) change unless otherwise stated
[b] Haem-A-QoL questionnaire is specific to assessment of adults (≥17 years)
[c] Refers to change from baseline after 6 months of factor prophylaxis during OP and after 6 months of marstacimab prophylaxis during ATP

[d] Refers to change from baseline after 6 months of factor prophylaxis during OP and after 12 months of marstacimab prophylaxis during ATP
[e] Effect Size (ES) is calculated as [estimated median difference] / (Standard Deviation [SD] at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.
[f] Haemo-QoL questionnaire is specific to assessment of adolescents 12 to <17 years
[g] Non-inferiority criterion for the EQ-5D-5L index was lower bound of 95% CI > -0.1; it was lower bound of 95% CI > -9.5 for the EQ-VAS.
[h] Higher scores indicate better health states with the maximum value of 1 (EQ-5D-5L index score ranges from -0.594 to 1). UK look-up value was applied to all participants. Measures the participant's self-rated health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).
[i] Measures the participant's self-rated health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).
[j] Per p.114 of the BASIS Interim Clinical Study Report, PGIC-H was not included in the testing hierarchy to control type I error rate within each statistical objective. The PGIC-H measured the participant's overall impression of change in their life with haemophilia in a 7-point ordinal scale with lower scores indicating better change; 1: greatly improved, 2: moderately improved, 3: slightly improved, 4: no change, 5: slightly worsened, 6: moderately worsened, and 7: greatly worsened.
[k] HAL2 questionnaire is specific to assessment of adults (≥17 years). Per p.115 of the BASIS Interim Clinical Study Report, HAL2 was not included in the testing hierarchy to control type I error rate within each statistical objective. Each of the total, component, or domain scores of HAL2 range from 0 to 100, with higher scores indicating better functional status.
[l] pedHAL questionnaire is specific to assessment of adolescents 12 to <17 years. Per p.115 of the BASIS Interim Clinical Study Report, pedHAL was not included in the testing hierarchy to control type I error rate within each statistical objective. Each of the total, component, or domain scores of pedHAL range from 0 to 100, with higher scores indicating better functional status.

Overall conclusion for clinical claims

The ADAR presented clinical claims as follows:

In adolescents and adults aged 12 years and older with severe HMA (FVIII < 1%) without inhibitors:

- Marstacimab has superior efficacy to extended half-life (EHL) FVIII prophylaxis and non-inferior efficacy to emicizumab with respect to the control of bleeding events; and
- Marstacimab has a non-inferior safety profile to EHL FVIII prophylaxis and emicizumab in terms of adverse events.

In adolescents and adults aged 12 years and older with severe HMB (FIX < 1%) without inhibitors:

- Marstacimab has superior efficacy to EHL FIX prophylaxis with respect to the control of bleeding events; and
- Marstacimab has a non-inferior safety profile to EHL FIX prophylaxis in terms of adverse events.

Based on the primary efficacy analysis, which included a subanalysis to present data on treated ABRs for HMA and HMB, it can be concluded that:

- Treatment of HMA with marstacimab compared favourably with FVIII prophylaxis, but the results are optimistic given the patient cohort in the key trial had 73.6% of patients treated with SHL products rather than EHL products. This is different to the current Australian clinical context where majority of patients on factor prophylaxis receive EHL products.
- In the treatment of HMA, the available data suggest that the efficacy (based on total ABR) of marstacimab is non-inferior to emicizumab, though this conclusion is based on highly uncertain results of the indirect treatment comparison subject to geographical and temporal differences between the trials and unmeasured confounding.
- Treated ABRs for HMB were similar on average between people receiving FIX prophylaxis or marstacimab with half of these people having no clinically important reductions in the number of bleeds that required treatment. The applicant's claim of superior efficacy was not substantiated.

The ADAR provided a combined safety analysis for the HMA and HMB populations in which claims of non-inferior safety for marstacimab compared separately to FVIII and FIX were not demonstrated. The available pooled safety data (Table 4) indicate differences in the occurrence of reported adverse events (AEs) and serious adverse events (SAEs) in the observational and active treatment phases of the BASIS trial, where factor prophylaxis and marstacimab were compared.

13. Economic evaluation

The ADAR presented two economic analyses. A cost-minimisation approach (CMA) was presented for marstacimab against emicizumab for adolescents and adults aged ≥12 years with severe HMA without inhibitors. The commentary considered that this was reasonable and consistent with the non-inferiority claim for marstacimab versus emicizumab in patients with HMA.

A separate cost-utility analysis (CUA) for marstacimab against factor prophylaxis was also presented for adolescents and adults aged 12 years and older with severe HMA or HMB without inhibitors based on the BASIS trial. The commentary considered this was not appropriate as:

- PASC had advised that the ADAR should present two separate economic analyses for each the HMA and HMB populations, not an analysis which pools the HMA and HMB populations together.
- PASC advised that a CUA for the HMB population was only appropriate if the ADAR was able to demonstrate superiority in comparison to EHL prophylaxis for the HMB population. As raised above (12. Overall conclusion for clinical claims), this was not demonstrated. If superiority against EHL prophylaxis could not be demonstrated from the BASIS trial for the HMB population, PASC considered that the most appropriate economic evaluation for this population would be a CMA. This analysis was performed during the evaluation and is presented below.
- The commentary considered that given the ease of administration of emicizumab over EHL FVIII prophylaxis (subcutaneous versus intravenous injections), patients who have not switched over to emicizumab are unlikely to switch to marstacimab, noting its similarity in administration frequency and method (subcutaneous) and safety. Consistent with this, the ADAR assumed that no patients with HMA currently undergoing factor prophylaxis would switch to marstacimab (see 14. Financial/budgetary impacts). The commentary noted that this underscores that the main comparator for the HMA population is emicizumab, and the irrelevance of presenting a CUA for patients with HMA compared to factor prophylaxis.

HMA CMA

The key inputs from the CMA for marstacimab vs emicizumab in patients with HMA presented in the ADAR are presented Table 12.

Table 12 Key inputs for the HMA CMA, marstacimab vs emicizumab

Input	Value/Source	Comment
Time horizon	One week.	The PBAC recommend conducting CMAs over two years when there is a loading dose in the initial year (paragraph 6.65, ravulizumab PSD, July 2021 PBAC Meeting).
Average weight	77.8 kg. Weighted average based on the distribution of weights for HMA and HMB patients in the ABDR Annual Report.[13]	The inclusion of HMB patients to determine the average weight was not reasonable. The average weight for HMA patients was 75.2kg.
Marstacimab dose	300 mg loading dose, followed by 150 mg flat dosing (standard) or 300 mg for those who have a dose escalation once per week based on the Marstacimab PI.	The ADAR has not included the loading dose in the CMA which was not appropriate.
Emicizumab dose	1.5 mg/kg once per week as per the Emicizumab PI.	This was reasonable.
Proportion of marstacimab patients with dose escalations	4.7%, derived from BASIS.	Data from the BASIS LTE study suggest that 14% of patients had dose escalations. The Commentary considered this a better estimate as the observational period was longer and the mean dose appears to not include the initial loading dose.
Marstacimab treatment compliance	98%, sourced from BASIS.	This data was based on the pooled HMA and HMB population.
Emicizumab treatment compliance	100%	It may not be reasonable to assume perfect treatment compliance. This has been tested in sensitivity analyses.
Marstacimab cost	$**redacted** per 150 mg pen.	Proposed price.
Emicizumab cost	$95.99 per mg (US published price).	This was an assumed price for emicizumab. The CMA with the effective price of emicizumab has been presented in the CIC section of the Executive Summary.

Source: Constructed during the evaluation.
ABDR = Australian Bleeding Disorders Registry; CIC = Committee in Confidence; CMA = cost-minimisation approach; CSR = clinical study report; PBAC = Pharmaceutical Benefits Advisory Committee; PI = product information; PSD = Public Summary Document; US = United States.

The result of the CMA is presented in Table 13. These results should be interpreted with caution as the price for emicizumab has been assumed by the ADAR. The results using the effective price of emicizumab are presented in the Committee in Confidence section. The ADAR has not proposed it would adjust the price of marstacimab to ensure it is cost-minimised against the effective price of emicizumab.

[13] National Blood Authority Australia. Annual Report 2024 -2025. 2025.

Table 13 Results of the HMA CMA, marstacimab vs emicizumab

	Marstacimab	Emicizumab
Average dose per week	157 mg[a]	117 mg[b]
Treatment compliance	98%	100%
Dose per week after compliance	154 mg	117 mg
Cost per week	$**redacted**	$11,206

Source: Constructed during the evaluation from the "Economic inputs – marstacimab final" Excel workbook provided with the ADAR.
ADAR = Applicant Developed Assessment Report; CMA = cost-minimisation approach; CSR = clinical study report; PI = product information
[a] The ADAR assumed 4.7% of patients had a dose escalation of 300 mg and the remaining 95.2% had the standard 150 mg dose.
[b] Average weight of 78 kg multiplied by PI dose of 1.5 mg/kg

The CMA was conducted over the course of one maintenance week. The Commentary considered that this was not appropriate as marstacimab requires an initial loading dose. Previous CMAs submitted to the Pharmaceutical Benefits Advisory Committee's (PBAC) with loading doses in Year 1 were noted to have conducted the CMA over the first two years of treatment (i.e. including the loading dose) (paragraph 6.65, ravulizumab PSD, July 2021 PBAC Meeting).

The Commentary presented a CMA over two years with the results reported in Table 14.

Table 14 Results of the CMA over two years presented in the Commentary

	Marstacimab	Emicizumab
Loading dose	300 mg	N/A
Cost for loading dose	$**redacted**	
Maintenance dose	157 mg[a]	117 mg[b]
Average maintenance dose cost	$**redacted**	$11,206
Number of standard maintenance doses in Year 1	51	52
Number of standard maintenance doses in Year 2	52	52
Compliance rate	98%	100%
Average number of standard maintenance doses in Year 1 (i.e. adjusted for compliance)	50	52
Average number of standard maintenance doses in Year 2 (i.e. adjusted for compliance)	51	52
Total maintenance doses over two years	101	104
Total cost in Year 1	$**redacted**	$582,724
Total cost in Year 2	$**redacted**	$582,724
Total cost over two years	$**redacted**	$1,165,448

Source: Constructed during the evaluation from the "Economic inputs – marstacimab final" Excel workbook provided with the ADAR.
ADAR = Applicant Developed Assessment Report; CMA = cost-minimisation approach; CSR = clinical study report; PI = product information.
[a] The ADAR assumed 4.7% of patients had a dose escalation of 300 mg and the remaining 95.2% had the standard 150 mg dose.
[b] Average weight of 78 kg multiplied by PI dose of 1.5 mg/kg

The Commentary considered that the main area of uncertainty in the CMA related to the proportion of marstacimab patients with dose escalations. The base case estimate was derived from the mean dose in the BASIS trial (157 mg), however this was not appropriate as it includes the initial loading dose which all patients receive. The Commentary considered that a better estimate for the proportion of patients receiving dose escalation may come from BASIS LTE as

the observational period was longer and the mean dose appears to not include the initial loading dose. The mean dose per administration was reported to be 170.8 mg in BASIS LTE. This results in approximately 14% of patients having dose escalations, noting that this proportion may further increase over time. This parameter was tested in sensitivity analyses (Table 15).

The ADAR did not present any sensitivity analyses for the HMA CMA. Sensitivity analyses were presented in the Commentary around the CMA results over the first two years of treatment using the price of emicizumab assumed by the ADAR (Table 15). These analyses have been replicated using the effective price of emicizumab in the Committee in Confidence section.

Table 15 Sensitivity analyses conducted on the HMA CMA

Analyses	Cost over two years		Absolute price difference (Marstacimab – emicizumab cost)	% Change
	Marstacimab	Emicizumab		
Base case	$**redacted**	$1,165,448	-$**redacted**	0%
Average weight (base case: 77.8kg, HMA and HMB patients)				
• 75 kg (HMA patients in ABDR report)	$**redacted**	$1,126,808	-$**redacted**	-5%
Proportion of marstacimab patients receiving dose escalations (base case: 4.7%)				
• 13.9% (BASIS LTE)	$**redacted**	$1,165,448	-$**redacted**	-6%
Marstacimab compliance (base case: 98%)				
• 100%	$**redacted**	$1,165,448	-$**redacted**	-1%
• 95%	$**redacted**	$1,165,448	-$**redacted**	2%
Emicizumab compliance (base case: 100%)				
• 98%	$**redacted**	$1,142,139	-$**redacted**	-3%
• 95%	$**redacted**	$1,107,175	-$**redacted**	-8%

Source: Constructed during the evaluation from the "Economic inputs – marstacimab final" Excel workbook provided with the ADAR.
ABDR = Australian Bleeding Disorders Registry; ADAR = Applicant Developed Assessment Report; CMA = cost minimisation approach; HMA = haemophilia type A; LTE = long-term extension

HMB CMA

As mentioned above, the ADAR did not present a CMA for marstacimab versus EHL prophylaxis in the HMB population which was not appropriate as superiority was not demonstrated (see 12. Overall conclusion for clinical claims). This was conducted by the Commentary.

Key inputs for the CMA conducted during the evaluation are presented in Table 16, where possible these were sourced from the Applicant's HMA CMA and the CUA.

Table 16 Key inputs used in the cost-minimisation approach, marstacimab vs EHL Factor IX, conducted by the Commentary

Input	Value/Source	Comment/justification
Time horizon	Two years	PBAC precedent (paragraph 6.65, ravulizumab PSD, July 2021 PBAC Meeting).
Average weight	79.2 kg based on the weighted average based on the distribution of weights of HMB patients in the ABDR Annual Report.	Given that EHLs are priced per IU, using the average weight as opposed to a distribution of body weights was appropriate.
Marstacimab dose	300 mg loading dose, followed by 150 mg flat dosing (standard) or 300 mg for those who have a dose escalation once per week based on the Marstacimab PI.	
EHL factor prophylaxis dose	2,876 IU/kg/year	ABDR utilisation data included with the ADAR.[a]
Proportion of marstacimab patients with dose escalations	4.7% derived from the BASIS trial.	As noted in the HMA CMA, the derivation included the initial loading dose, which the commentary did not consider to be appropriate. However, to ensure consistency with the ADAR's HMA CMA, 4.7% has been applied, with estimate sourced from BASIS LTE tested in sensitivity analyses.
Marstacimab treatment compliance	98% sourced from the BASIS trial.	Similar to above, this data was based on the pooled HMA and HMB population. .
Marstacimab cost	$**redacted** per 150 mg pen.	Proposed price.
EHL cost	$0.68 per IU sourced from the ADAR's assumed price in the CUA.	The effective price has been tested in the CIC section of the Executive Summary
EHL dosing frequency	Once per week.	Median prescribed injections per week reported in Australian real-world utilisation study[14]
EHL Factor IX administration costs	$643 (ADAR CUA, NHCDC code 20.10)	This has been tested in sensitivity analyses.

Source: Constructed during the evaluation.
ABDR = Australian Bleeding Disorders Registry; CIC = Committee in Confidence; CMA = cost-minimisation approach; CSR = clinical study report; EHL = extended half-life; HMA = haemophilia type A; HMB = haemophilia type B; NHCDC = National Hospital Cost Data Collection; PBAC = Pharmaceutical Benefits Advisory Committee; PI = product information; PSD = Public Summary Document
[a] ABDR utilisation data for severe HMB patients aged 12+

The results of the HMB CMA are presented in Table 17.

[14] Brennan, Y, Parikh, S, McRae, S & 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*, vol. 26, no. 3, 2020/05/01, pp. 529-535.

Table 17 Results of the CMA over two years

	Marstacimab	EHL Factor IX
Loading dose	300 mg	N/A
Cost for loading dose	$**redacted**	
Maintenance dose	157 mg[a]	4,378 IU[b]
Average maintenance dose cost	$**redacted**	$2,977
Number of standard maintenance doses in Year 1	51	52
Number of standard maintenance doses in Year 2	52	52
Compliance rate	98%	100%[c]
Average number of standard maintenance doses in Year 1 (i.e. adjusted for compliance)	50	52
Average number of standard maintenance doses in Year 2 (i.e. adjusted for compliance)	51	52
Total maintenance doses over two years	101	104
Cost per administration	$0	$643
Administration costs over two years	$0	$67,102
Marstacimab/factor costs over two years	$**redacted**	$310,663
Total cost in Year 1	$**redacted**	$188,882
Total cost in Year 2	$**redacted**	$188,882
Total cost over two years	$**redacted**	$377,765

Source: Constructed during the evaluation from the "Economic inputs – marstacimab final" Excel workbook provided with the ADAR.
ADAR = Applicant Developed Assessment Report; CMA = cost-minimisation approach; CSR = clinical study report; EHL = extended half life; PI = product information
[a] The ADAR assumed 4.7% of patients had a dose escalation of 300 mg and the remaining 95.2% had the standard 150 mg dose.
[b] Average weight of 79 kg multiplied by real world utilisation dose of (2,876 IU/kg/year)/52 administrations per year.
[c] Compliance already captured in real world utilisation data.

The main area of uncertainty associated with the HMB CMA relates to the dosing of EHL prophylaxis given that it is tailored to individual patients' clinical response. The Commentary has used the average dose per kg per year reported in the ABDR data provided by the ADAR for patients with severe HMB aged 12 or older undergoing prophylaxis (2,876 IU/kg/year, 55 IU/kg/week). This is assumed to include treatment compliance. A limitation of this source is that it likely includes both SHL and EHL use. However, given this data was collected in June 2024, it may be reasonable to assume the vast majority of these patients are using EHLs (as it is assumed in the ADAR's CUA). It is also likely that this dose may be overestimated as it includes additional factor use for breakthrough bleeds, however this impact is also likely to be minimal.

An alternative dosing estimate sourced from Brennan et al. (2020)[14] (51.4 IU/kg/week) has been tested in sensitivity analyses (Table 18). This estimate is also derived from the ABDR database and includes only EHL usage, however only 83% of the study population had severe HMB and 7% were receiving on demand therapy as opposed to prophylaxis.

Similar to the HMA CMA, the proportion of marstacimab patients with dose escalations is also an area of uncertainty which has been tested in sensitivity analyses.

In line with the CUA, the Commentary assumed the cost of factor administration was based on a consultation with a haematologist (non-admitted code 20.10), however a considerable portion of this cost ($291) was noted to be direct pharmacy costs, which may not apply given that factor product has been accounted for separately. Additionally, administration may also be conducted under the guidance of a haematology clinical nurse specialist (non-admitted code 40.48) or be self-administered. This was tested in sensitivity analyses (Table 18).

Sensitivity analyses conducted on the HMB CMA are presented in Table 18.

Table 18 Sensitivity analyses conducted on the HMB CMA

Analyses	Cost over two years		Absolute price difference (Marstacimab – EHL cost)	% Change
	Marstacimab	EHL		
Base case	**$redacted**	$377,765	**$redacted**	0%
Average weight (base case: 79.2kg, HMB patients in ABDR report)				
• 75 kg	**$redacted**	$361,461	**$redacted**	20%
Proportion of marstacimab patients receiving dose escalations (base case: 4.7%)				
• 13.9% (BASIS LTE CSR)	**$redacted**	$377,765	**$redacted**	47%
Marstacimab compliance (base case: 98%)				
• 100%	**$redacted**	$377,765	**$redacted**	11%
• 95%	**$redacted**	$377,765	**$redacted**	-17%
EHL dose (base case: 55 IU/kg every week, based on ABDR data[a])				
• Mean annual dose in Brennan et al. (2020)[14] (51.4 IU/kg/week)	**$redacted**	$355,815	**$redacted**	26%
• 100 IU/kg every 10 days (upper PI dose)[b]	**$redacted**	$440,161	**$redacted**	-75%
• 50 IU/kg every 7 days (lower PI dose)[b]	**$redacted**	$347,951	**$redacted**	36%
EHL Factor IX administration cost (base case: $643, NHCDC code 20.10)				
• $352 ($291 of pharmacy costs removed)	**$redacted**	$347,397	**$redacted**	36%
• $452 (code 40.48, haematology clinical nurse specialist consult)	**$redacted**	$357,833	**$redacted**	24%
• $0 (self-administered)	**$redacted**	$310,663	**$redacted**	80%

Source: Constructed during the evaluation from the "Economic inputs – marstacimab final" Excel workbook provided with the ADAR.
ABDR = Australian Bleeding Disorders Registry; ADAR = Applicant Developed Assessment Report; CMA = cost-minimisation approach; EHL = extended half life; HMB = haemophilia type B; IU = international units; LTE = long-term extension; PI = product information
[a] Mean annual dose reported in ADBR data for HMB prophylaxis patients presented in the ADAR, note this may include SHL use.
[b] The eftrenonacog alfa PI recommended dosing of 50 IU/kg once weekly or 100 IU/kg once every 10 days.

HMA and HMB CUA

As mentioned above, the ADAR presented a CUA for a pooled HMA and HMB population based on the BASIS trial. The Commentary considered that this was not appropriate as PASC had advised that two separate economic evaluation needed to be presented for the HMA and HMB populations given that each population has different comparators.

Also as described above, PASC considered that a CUA for the HMB population was only warranted if superiority for marstacimab against EHL prophylaxis was demonstrated. However, the

Commentary considered that this was not demonstrated and hence the most appropriate economic evaluation for this population would be a CMA (as conducted during the evaluation above).

For the HMA population, the Commentary noted PASC advice that CMA against emicizumab (presented above) would be the most appropriate economic evaluation.

Given that the BASIS trial predominantly included patients with HMA (79% HMA versus 21% HMB), the use of pooled data from the BASIS trial infers that the treatment effect of marstacimab vs FVIII replacement in HMA applies to the effect of marstacimab treatment vs FIX replacement in HMB. The Commentary considered that, based on Section 12. Overall conclusion for clinical claims, this was not supported.

The Commentary considered that the following evaluation of the CUA should be interpreted in the context of these concerns.

They key components of the CUA are presented Table 19.

Table 19 Summary of the economic evaluation

Component	Description
Perspective	Health care system perspective
Population	Australian adolescents and adults aged 12 years and older with severe HMA or HMB without inhibitors. The Commentary noted that this was not appropriate as PASC had advised that separate economic evaluations should be presented for the HMA and HMB cohorts.
Comparator	HMA population: EHL Factor VIII prophylaxis HMB population: EHL Factor IX prophylaxis
Type(s) of analysis	Cost-utility analysis
Outcomes	Quality-adjusted life years
Time horizon	Lifetime (66 years as patients enter the model at 33 years). The Commentary noted that this assumption reflects the mean age of the population in the key trial. The Commentary noted that the limited subgroup analysis from the trial does suggest that there may be a difference in treatment effect in younger patients, however the data from the trial used in the model are not available by subgroup (as these are based on post-hoc analyses of trial data), and so the Commentary could not test the impact of this assumption.
Computational method	Decision tree followed by Markov cohort model
Health states	Decision tree outcomes: • <5 6-month bleeding rate group • ≥5 6-month bleeding rate group Markov cohort model health states: • Experiencing target joint bleed • Chronic haemophilic arthropathy • Dead
Cycle length	Six months

<table>
<tr><th>Component</th><th>Description</th></tr>
<tr><td>Outcome and transition probabilities</td><td>
Decision tree:
Patients were assigned to each 6-month bleeding rate group based on the distribution observed in the BASIS trial and the BASIS LTE. The Commentary noted once patients are assigned to their bleeding rate group at model entry, they can no longer switch back. The Commentary considered this assumption was not justified and was not reasonable.
<table>
<tr><th></th><th><5 6-month bleeding rate group</th><th>≥5 6-month bleeding rate group</th></tr>
<tr><td>Factor prophylaxis</td><td>75.9%</td><td>24.1%</td></tr>
<tr><td>Marstacimab</td><td>89.5%</td><td>10.5%</td></tr>
</table>
Markov model:
Within each bleeding rate group, patients could experience a target joint bleed each cycle where the probabilities were based off the BASIS trial, and were treatment arm and bleeding rate group specific. The ADAR had assumed an ongoing treatment benefit in terms of a reduction in target joint bleeds associated with marstacimab treatment for the duration of the model. The Commentary considered this was not well justified and was highly uncertain.
<table>
<tr><th></th><th><5 6-month bleeding rate group</th><th>≥5 6-month bleeding rate group</th></tr>
<tr><td>Factor prophylaxis</td><td>3.2%</td><td>55.0%</td></tr>
<tr><td>Marstacimab cycle 1</td><td>2.9%</td><td>71.4%</td></tr>
<tr><td>Marstacimab cycle 2</td><td>2.0%</td><td>58.3%</td></tr>
<tr><td>Marstacimab cycle 3</td><td>4.1%</td><td>44.4%</td></tr>
<tr><td>Marstacimab cycle 4</td><td>2.2%</td><td>18.2%</td></tr>
<tr><td>Marstacimab cycle 5+</td><td>2.8%</td><td>9.1%</td></tr>
</table>
Among patients who are experiencing target joint bleeds, 20% were assumed to develop chronic haemophilic arthropathy derived from Zhang et al. (2025).[15] The Commentary noted the ADAR had applied the probability of developing chronic haemophilic arthropathy per target joint in Zhang et al. (2025)[15] to the proportion of patients experiencing any target joint bleed based on the BASIS data. The Commentary considered this approach was not appropriate because the risk of arthropathy was based on a single joint. By applying a per-joint risk to the proportion of patients with any target joint bleed, the model overestimated the probability of developing arthropathy.

An SMR of 2.4 was applied to patients in all health states to inform mortality sourced from Hassan et al. (2021).[16]
</td></tr>
<tr><td>Discount rate</td><td>5% for costs and outcomes.</td></tr>
<tr><td>Software</td><td>TreeAge Pro and Excel</td></tr>
</table>

Source: Constructed during the evaluation.
ADAR = Applicant Developed Assessment Report; EHL = extended half-life; HMA – haemophilia type A; HMB = haemophilia type B; LTE = long-term extension; PASC = PICO Advisory Committee; SMR = standardised mortality ratio.

The economic evaluation adopted a hybrid decision-tree and Markov cohort model structure. When patients enter the model, they are assigned to either a <5 or ≥5 6-month bleeding rate groups. The ADAR had justified this approach by stating that the greatest treatment benefit of

[15] Zhang L, Guo J, Wei S, Li J, Dou Y, Cheng T, et al. The prediction of haemophilic arthropathy progression based on MRI findings and clinical characteristics. Orphanet Journal of Rare Diseases. 2025 2025/04/18;20(1):190.

[16] Hassan S, Monahan RC, Mauser-Bunschoten EP, van Vulpen LFD, Eikenboom J, Beckers EAM, et al. Mortality, life expectancy, and causes of death of persons with hemophilia in the Netherlands 2001-2018. J Thromb Haemost. 2021 Mar;19(3):645-53.

marstacimab was observed in patients who had bleeding rates of ≥5 during the 6-month OP of BASIS (i.e. when they were on factor prophylaxis). The Commentary considered that this justification was not appropriate given that the probabilities of being assigned to each of these outcomes across the two treatment arms were not based on the distribution observed during the OP phase but were treatment-arm specific. The Commentary noted that in the ADAR's model a greater proportion of patients were assigned to the <5 6-month bleeding rate group in the marstacimab arm compared to the factor prophylaxis arm and as patients do not transition between bleeding rate groups, this assumes an ongoing treatment effect associated with marstacimab.

Once separated by bleed rate, patients enter the Markov model which has three health states: no arthropathy, chronic haemophilic arthropathy and dead. All patients enter the model in the no arthropathy health state, and within each six-month cycle have a treatment-specific probability of experiencing a target joint bleed. The probability of target joint bleeds on factor prophylaxis was based on the six-month observation period of BASIS. The Commentary noted that despite the short observation period, the assumption of patients experiencing steady-state in the OP of BASIS was reasonable (i.e., patients were considered to have stable disease during the OP of BASIS). For the marstacimab arm, the probabilities for the first two years of treatment were time-dependent and were derived from the BASIS trial. Beyond this time the ADAR assumed that an ongoing treatment effect associated with marstacimab was maintained until the end of the time horizon (66 years versus two years of data from BASIS and BASIS LTE used in the model). The Commentary considered that the assumption of long-term treatment effect maintenance was not well justified, and the model structure did not allow for a waning of the treatment effect to be explored. Given this limitation a shorter time horizon was explored in sensitivity analyses (see Table 22).

In either model arm, upon experiencing a target joint bleed, this could resolve, or patients could progress to the chronic haemophilic arthropathy. Patients were assumed to remain in this health state until death. The Commentary considered that this was inconsistent with existing literature as other economic models include temporary cures for this health state through joint replacement surgeries.[17,18]

In all health states patients were assumed to be at-risk of death, with a standardised mortality ratio of 2.4 (for severe haemophilia patients reported in Hassan et al. (2021)[16]) applied to Australian life tables. The Commentary considered that this was reasonable.

The Commentary noted that the number of treated bleeds or the relative difference in the annual treated bleeding rate, which was the primary efficacy endpoint in of the BASIS trial was not directly modelled to determine the effectiveness of treatment. Only the proportion of patients experiencing target joint bleeds which appeared to be a post-hoc analysis and not statistically significant was used to model the treatment effectiveness of marstacimab. This structural approach resulted in the proportion of patients with target joint bleeds being independently modelled from the incidence of bleeds. This was not justified in the ADAR, and the Commentary considered that this was inappropriate as it did not allow the impact of variations in baseline bleed rates to be explored. Given the applicability concerns of the BASIS trial in terms of

[17] Institute for Clinical and Economic Review 2020, Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A without Inhibitors: Effectiveness and Value https://icer.org/wp-content/uploads/2020/10/ICER_Hemophilia-A_Final-Report_112020.pdf

[18] Institute for Clinical and Economic Review 2022, Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value <https://icer.org/wp-content/uploads/2022/05/ICER_Hemophilia_Final_Report_12222022.pdf.

annualised bleed rates expected in practice, the Commentary considered that this was not reasonable.

Treatment-specific inputs from the BASIS trial were assumed to apply to the modelled population without adjustment, including the proportion of patients with <5 or ≥5 bleeds per six-months and the six-month probabilities of target joint bleeds. The Commentary noted a number of concerns regarding the applicability of the BASIS trial data to the proposed setting:

- Bleed rates on factor prophylaxis in BASIS were higher than that would be expected in the proposed setting. The Commentary considered this was likely due to i) the use of SHL rather than the EHL products more commonly used in Australia; and ii) the settings in which the trials were conducted (low-middle income countries), which may not have the resources able to prioritise bleed minimisation. While unit costs per IU of factor prophylaxis were adjusted in the model to reflect EHL use, the ADAR did not adjust the amount of factor used or bleed rates. Real-world data do support a reduction in the annual number of bleeds following the switch from SHL to EHL products in the Australian setting, due to improved compliance to EHL treatment (Brennan et al. 2020).[14]
- The ADAR pooled the HMA and HMB treatment effect together in the economic model. As raised previously, the commentary did not consider this to be appropriate. The Commentary considered that there may be differences across patients with HMA and HMB in terms of baseline bleed rates, effect of marstacimab treatment and factor use. Furthermore, the distribution of patients with HMA vs HMB in the BASIS trial (79% HMA and 21% HMB) was different to that would be expected in the Australian setting (87% HMA and 13% HMB). While the ADAR adjusted factor use for the distribution of patients with HMA and HMB expected in practice, the distribution of patients across high and low bleeds, or subsequent probability of target joint bleeds were not adjusted.
- The derivation of transition probabilities for outcomes in the marstacimab arm includes patients who were treated with on-demand factor replacement during the observational phase of BASIS. This was not appropriate as these patients would have different baseline risks than patients who received factor prophylaxis and have been rightly excluded from the comparator arm. This may overestimate the effectiveness in the intervention arm as patients who have more stable baseline disease are excluded from the comparator arm but included in the intervention arm.

The Commentary noted that translations studies were not presented in the ADAR to examine these applicability issues and determine the most appropriate approach to model the treatment effect expected in Australian clinical practice. The Commentary considered that using local data on the annual number of bleeds on factor prophylaxis and applying the treatment effect of marstacimab in terms of reducing bleeds from BASIS may be a more appropriate approach.

The Commentary also identified other uncertainties regarding the proportion of marstacimab patients having dose escalations and costs associated with factor administration. These have been discussed in the CMA sections. Additionally, it is unclear if factor use in the comparator arm was double counted, as the annual factor dose reported in the BASIS CSR included all factor consumption, possibly covering breakthrough bleeds, which were also counted separately in the model. These were tested in sensitivity analyses (Table 22). The results of the economic analysis are presented in Table 20. The ADAR did not present a stepped analysis which was not reasonable given the uncertainty associated with long-term assumptions and inputs which were not observed during the key trial.

Table 20 Base case results of the economic evaluation

	Marstacimab	Factor prophylaxis	Increment
Total cost of prophylaxis	$**redacted**	$2,683,091	$**redacted**
Total cost of breakthrough bleeds	$173,470	$407,993	−$234,523
Total costs	**$redacted**	**$3,091,084**	**$redacted**
QALYs without chronic haemophilic arthropathy	12.450	10.478	1.972
QALYs with chronic haemophilic arthropathy	2.244	3.588	−1.345
Total QALYs	**14.694**	**14.066**	**0.628**
Incremental cost per additional QALY gained over a lifetime time horizon:			**$redacted**

Source: Table 48 of the ADAR
ADAR = Applicant Developed Assessment Report; QALY = quality-adjusted life year

The key model drivers are presented in Table 21.

Table 21 Key drivers of the model

Description	Method/Value	Impact Base case: $redacted /QALY gained
Splitting patients into different bleeding rate groups	The model separates patients based on their bleeding rate (observed in the trial) for the entire duration of the model. This is associated with substantial uncertainty as once patients are assigned their bleeding rate group at model entry, they can no longer switch back. In the Australian setting, a higher proportion of patients would be expected in the <5 bleed rate group (equivalent to ABR of <10) than assumed in the base case.	*High, favours marstacimab. Assuming all patients have bleeding rates of <5 per six months increases the ICER to $***redacted** */QALY gained.*
Chronic haemophilic arthropathy health state	The model assumes 20% of patients experiencing target joint bleeds enter the chronic haemophilic arthropathy health states which is associated with poorer utilities and do not recover. The assumption that patients do not recover from arthropathy is uncertain and was not justified. Other economic models assume temporary cure of chronic arthropathy due to joint replacement surgeries.	*High, favours marstacimab. Excluding this health state increased the ICER to $***redacted** */QALY gained.*
Factor administration costs	$643 based on NHCDC code 20.10 (non-admitted hematology consultation). Administration may occur under the guidance of a hematology clinical nurse specialist (code 40.48, cost $453).	*High, favours marstacimab. Assuming nurse administration increased the ICER to $***redacted** */QALY gained.*
Proportion of marstacimab patients with dose escalations	4.7% based on the BASIS CSR. As raised in the CMA section, a better estimate may come from the BASIS LTE CSR where the mean dose (171 mg) does not include the initial loading dose. This results in approximately 14% of patients having dose escalations, noting that this proportion may further increase over time.	*High, favours marstacimab. Assuming 14% of patients have dose escalations increased the ICER to $***redacted** */QALY gained.*

Source: Constructed during the evaluation.
ABR = annual bleeding rate; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

The key sensitivity analyses conducted during the evaluation are presented in Table 22.

Table 22 Key sensitivity analyses performed on the CUA

Analyses	Inc. Cost	Inc. QALYs	ICER	% Change
Base case	**$redacted**	0.628	**$redacted**	0%
Discounting (base case: 5% to costs and outcomes)				
• 0%	**$redacted**	1.525	**$redacted**	-3%
• 3.5%	**$redacted**	0.786	**$redacted**	-1%
Time horizon (base case: 66 years)				
• 10 years	**$redacted**	0.260	**$redacted**	13%
Splitting patients into different bleeding rate groups (base case: included)				
• All patients are assigned to the <5 six month bleeding rate group ***#1***	**$redacted**	0.039	**$redacted**	1500%
Difference in % of patients with target joint bleeds in the <5 6MBR health state across treatments (base case: difference assumed)				
• No difference across treatment arms ***#2***	**$redacted**	0.597	**$redacted**	5%
% of patients with target joint bleeds in the ≥5 6MBR health state beyond the observed period (base case: 9.1%)				
• 18.2% (last observed data point in BASIS)	**$redacted**	0.593	**$redacted**	6%
• 55% (comparator arm in BASIS)	**$redacted**	0.516	**$redacted**	22%
Chronic haemophilic arthropathy health state (base case: included)				
• Excluded	**$redacted**	0.361	**$redacted**	74%
% of patients with marstacimab dose escalations (base case: 4.7%, BASIS)				
• 14%, BASIS LTE	**$redacted**	0.628	**$redacted**	34%
Factor administration cost (base case: $643)				
• $0 (self-administration)	**$redacted**	0.628	**$redacted**	122%
• $352 ($291 of pharmacy costs removed)	**$redacted**	0.628	**$redacted**	55%
• $453 (nurse consult)	**$redacted**	0.628	**$redacted**	36%
Cost of breakthrough bleeds (base case: based on international dosing recommendations)				
• Exclude factor cost from comparator arm (keep administration costs)	**$redacted**	0.628	**$redacted**	13%
Multivariate analyses				
#1, #2	**$redacted**	0.000	Dominated	

Source: Constructed during the evaluation from the "Economic inputs – marstacimab final" Excel workbook provided with the ADAR.
ADAR = Applicant Developed Assessment Report; EHL = extended half-life; ICER = incremental cost-effectiveness ratio; LTE = long-term extension; MDT = multidisciplinary team; QALYs = quality-adjusted life year; SMR = standardised mortality rate; 6MBR = six month bleeding rate

14. Financial/budgetary impacts

A combination of epidemiological and market-share approaches was used to estimate the total number of patients with severe HMA and HMB who will receive treatment with marstacimab. The patient cohort presented in the financial estimates was limited to males 12 years and older. The proposed listing is gender agnostic; however, the financial model only considers male patients 12 years and older. The Commentary considered that this approach is appropriate as most patients with severe HMA or HMB are male. Females accounted for 0.48% of patients attending

haemophilia treatment centres in the United States from January 2012 through September 2020 with factor levels known[19].

The prevalent patients treated for HMA and HMB were drawn from the ABDR 2023-24 data, extrapolated to cover the period 2026-27 to 2031-32 using the ABS population growth projections provided in the medium growth series. This approach applied the overall population growth rate, rather than growth rate for males 12 years and older. The Commentary considered that this would underestimate the growth rate of the population as the narrower population is growing more rapidly than the overall Australian population

Patient mortality is drawn from the ABS life tables and is applied in 5-year age brackets. The Commentary considered that this was an appropriate source of mortality rates. Incident patients were derived by applying the mortality rate to the change in prevalent population.

Using the incident and prevalent patient population, the financial model used a market-share approach to determine the number of incident patients with HMA who will receive marstacimab or emicizumab and incident patients with HMB who will receive marstacimab or FIX.

The financial model applied a market-share approach to determine the number of prevalent patients with HMA who would switch from FVIII to emicizumab and marstacimab. There were two errors (one population labelling and one in calculation logic) that were identified by the Commentary. The errors occur in the proportioning of patients with HMA between emicizumab and marstacimab. However, if emicizumab and marstacimab are cost-minimised (both medicine and administration costs), then these errors have no impact on the overall cost of listing marstacimab because the financial impact is the same regardless of which medicine is provided.

This approach was also applied to determine the number of prevalent patients with HMB who would switch from FIX to marstacimab. The Commentary noted that the calculations were correctly applied.

The financial model assumes that every patient who commences treatment does so at the beginning of the year which assumes that each patient will receive a full 12 months of treatment. The Commentary considered that while this approach when applied to large populations has a small effect (proportionately), in small patient populations, this may overestimate the number of patient years of treatment by approximately 50% in the first year of listing for incident patients. This impact will diminish over time as the proportion of continuing patients increase.

The financial model accounted for patients who require dose escalation consistent with the economic model (4.7%). However, this rate was significantly lower than the rate in the BASIS LTE trial (14%). The Commentary considered this underestimated the average cost of marstacimab treatment.

The financial model assumed that all patients would self-administer marstacimab. However, the Commentary considered that there may be a proportion of patients who are unwilling/unable to self-administer continuing to require administration by a healthcare professional. The Commentary considered this overestimated the administration saving associated with listing marstacimab.

The financial model calculated the number of administrations required in the first year of listing and then applied this rate across time. As the initial dosing rate is greater than the continuing dosing rate, the Commentary considered that this will overestimate the number of doses required for incident patients in the second and subsequent years. The Commentary also considered that

[19] Miller CH, Bean CJ. Genetic causes of haemophilia in women and girls. Haemophilia. 2021 Mar;27(2):e164-e179. doi: 10.1111/hae.14186. Epub 2020 Dec 13. PMID: 33314404; PMCID: PMC8132474.

this will overestimate the number of doses required for all prevalent patients who are beyond their first year of treatment.

The financial model applies the administration costs for the administration of FVIII and FIX based on all administration being carried out by haematologists. It is likely that a proportion of these administrations, particularly for patients with a stable condition, would be carried out by haematology clinical nurse specialists or be self-administered. As the largest financial component of listing marstacimab is savings associated with administration, this is likely to overestimate the savings that result from listing marstacimab. The commentary has tested various proportions of self-administration ($0 per administration) of FIX in a sensitivity analysis (Table 25).

As the effective price of emicizumab is not publicly known, the financial model assumed that the cost of emicizumab was equal to the proposed cost of marstacimab once it is listed. The financial impact of applying the effective price of emicizumab to the model is shown in the Committee-in-Confidence section.

The financial implications to the National Blood Agreement resulting from the proposed listing of marstacimab are summarised in Table 23.

Table 23 Financial implications of marstacimab to the National Blood Agreement

	2026/27	2027/28	2028/29	2029/30	2030/31	2031/32
Estimated use and cost of the proposed health technology						
People eligible for marstacimab – HMA/HMB	718	728	737	746	755	763
Patients with HMA						
Incident patients with severe HMA treated with marstacimab	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Remaining prevalent patients with severe HMA treated with marstacimab	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Total patients treated with marstacimab for HMA	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Patients with HMB						
Incident patients with severe HMB treated with marstacimab	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Remaining prevalent patients with severe HMB treated with marstacimab	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Total patients treated with marstacimab for HMB	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Total patients treated with marstacimab for HMA/HMB	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Total number of units dispensed [a]	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Cost to the National Blood Agreement [b]	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**

Source: Table 56 of the financial model provided with the submission.
[a] Assuming dose escalation, 1.05 doses per administration x 52 doses with compliance (98.08%) = 53.42 dose/patient/year
[b] Assumes $**redacted** per unit

Table 24 Changes in use and cost of other health technologies

	2026/27	2027/28	2028/29	2029/30	2030/31	2031/32
Change in use and cost of other health technologies						
Reduction in people who use emicizumab	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Change in cost of emicizumab [a]	-$2,139,206	-$3,020,417	-$8,660,031	-$6,386,489	-$11,794,768	-$8,148,117
Reduction in people who use FIX	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Change in FIX use [b]	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**
Cost of treating BTB for marstacimab patients (HMB) [c]	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**
Cost of treating BTB for FIX patients (HMB) [d]	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**
Net changes in other technologies costs to the National Blood Agreement	**-$redacted**	**-$redacted**	**-$redacted**	**-$redacted**	**-$redacted**	**-$redacted**
Administration costs						
Patients receiving marstacimab (HMB)	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Cost of administration for BTB ($1,505 per patient) [e]	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**
Cost of administration for FIX prophylaxis ($33,436 per patient) [f]	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**
Net change in administration costs	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**
Overall net financial impact of funding marstacimab[g]	**$23,936**	**$40,603**	**$66,187**	**$99,896**	**$133,831**	**$135,235**

Source: Table 58 of the financial model provided with the submission.
BTB = breakthrough bleed.
[a] Assuming dose escalation, 1.05 doses per administration x 52 doses with compliance (98.08%) = 53.42 dose/patient/year at $**redacted** per dose
[b] Assumes average patient weight of 77.83 kg and 3,578 IU/kg/year = 278,475.74 IU/patient/year at $0.68 per IU
[c] Assumes 2.48 breakthrough bleeds with a cost of $**redacted** (9,806 IU * $**redacted**)
[d] Assumes 3.26 breakthrough bleeds with a cost of $**redacted** (9,806 IU * $**redacted**)
[e] 0.78 BTB per year, assuming the cost per BTB of $1,929 (3 administrations at $643 each).
[f] 52 administration per year, assuming $643 per administration.
[g] Overall net financial impact of funding marstacimab = cost of marstacimab to the National Blood Agreement + net changes in other technologies costs to the National Blood Agreement + net changes in administration costs

The submission assumes that the number of breakthrough bleeds is the same for both emicizumab and marstacimab patients. The number of FVIII administration is also unchanged between the current and proposed scenarios. Therefore, there is no financial impact to administration costs for patients with HMA with the proposed listing of marstacimab.

For the patients with HMB, the financial impact to administration costs results from the reduction in breakthrough bleeds and FIX prophylaxis that occurs for patients who are treated with marstacimab. The submission expects patients to have 0.78 fewer breakthrough bleeds

annually (3.26 – 2.48). These patients will also no longer receive FIX which results in 52 less administrations annually.

The commentary has tested various proportions of self-administration ($0 per administration) of FIX in a sensitivity analysis (Table 25)

Table 25 Sensitivity analyses around net financial implications of marstacimab to the health system taking into account self-administration of FIX

	2026-27	2027-28	2028-29	2029-30	2030-31	2031-32
Net health system impact (base case) [a]	**$23,936**	**$40,603**	**$66,187**	**$99,896**	**$133,831**	**$135,235**
$0 per administration (i.e. 100% self-administration)	$525,528	$891,439	$1,453,163	$2,193,286	$2,938,328	$2,969,155
75% self-administration	$400,130	$678,730	$1,106,419	$1,669,939	$2,237,204	$2,260,675
50% self-administration	$274,733	$466,021	$759,675	$1,146,592	$1,536,079	$1,552,196

Source: Constructed during the evaluation.

[a] Base case assumes all administrations were conducted by a health care professional, at a cost of $643 per administration.

15. Other relevant information

Near market comparator for HMB

Uncertainty about the treatment effect of marstacimab for patients with HMB should be considered alongside other factors discussed in the ADAR. The ADAR has highlighted the potential advantage of reduced treatment burden and patient preference as the main value proposition and suggested that some patients may prefer the mode of administration and/or treatment frequency afforded by marstacimab. Arrangements under which clinicians and their patients with HMB nominate Factor IX prophylaxis or marstacimab based on individual treatment efficacy and/or convenience are also discussed in the ADAR.

The applicant's value proposition concerning patient preference and convenience of administration mode requires consideration within the broader clinical context of all available treatment options for HMB in Australia. Notably, there is evidence to suggest that the emergent treatment option of entranocogene dezaparvovec (ED), brand name Hemgenix®, is clinically superior to FIX for patients with severe HMB (Table 8). The additional benefit of ED over FIX, by extension, suggests the clinical effect of ED may be more favourable in comparison to marstacimab, which did not achieve treated ABR reductions as low as total ABR reductions for ED when either were compared with against FIX prophylaxis in the BASIS trials and HOPE-B study, respectively.

Treatment alternatives for HMA individuals who develop anti-emicizumab antibodies

Due to their mechanism of action, TFPI therapies provide an additional therapeutic option for an anticipated small number of individuals with HMA who have received emicizumab prophylaxis, but who develop anti-emicizumab antibodies and need to revert to intravenous factor replacement.

16. Committee-in-confidence information

Redacted

17. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- This application is requesting public funding for marstacimab to prevent bleeding in patients aged 12 years and over with severe Haemophilia A (HMA) or severe Haemophilia B (HMB), who are without Factor VIII or Factor IX inhibitors, respectively.
- Evidence for the comparison of marstacimab with emicizumab in HMA has been derived from an indirect treatment comparison and qualitative assessment of safety, between the BASIS and HAVEN 3 studies. ESC considered that there is low confidence in the results for both effectiveness and safety due to limitations with each study and the differences between them which impact the comparison. ESC considered adjustment by region may help account for differences in healthcare access and management across the two studies (noting that even with such adjustment uncertainties will remain).
- Most (73.6%) participants with HMA or HMB in the BASIS study used standard-half life (SHL) prophylaxis with Factor VIII (FVIII) or Factor IX (FIX) respectively. However, the ADAR's claim of superiority is against extended half-life (EHL) FVIII and FIX prophylaxis, which is the most-used form in Australia. Misalignment in the usage of SHL and EHL compared with the Australian setting may have resulted in an over-estimate of marstacimab effectiveness, as recent observational evidence suggests EHL is clinically superior (in ABR reductions and adherence) to SHL.
- Findings for secondary effectiveness and safety outcomes were based on a combined HMA and HMB population. Although the small sample size limits conclusions, there is a suggestion that ABR differs by haemophilia type. ESC requested the applicant present comparative safety information for the HMA and HMB populations separately for the purpose of the health technology assessment, as was advised by PASC.
- Concurrently, another application (MSAC 1805) is requesting public funding for a separate drug (concizumab) for patients aged 12 years and over with HMB, with or without inhibitors). In addition, etranacogene dezaparvovec ESC considered that both concizumab and etranacogene dezaparvovec (ED) (MSAC Application 1728.1, supported, but not yet funded for use) are near market comparators. ESC noted that no comparison has been made between marstacimab and either of these near-market comparators in the ADAR, although the commentary had conducted a preliminary assessment of comparative effectiveness against ED.

Economic issues:

- ESC identified several low confidence inputs used in the cost minimisation approach for the HMA and HMB populations and recommended respecifications for MSAC consideration.
- The ADAR presented a cost-utility analysis for a pooled HMA and HMB population with factor prophylaxis as the comparator. ESC considered that this was not appropriate as superiority of marstacimab versus FIX in the HMB population had not been established and the main comparator for HMA is emicizumab, not FVIII prophylaxis.
- The ADAR assumed that all patients would have their factor prophylaxis administered by a haematologist. It is likely that a proportion of patients will be self-administering, or will

have their treatment administered by a haematology clinical nurse specialist. Therefore, the ADAR's estimated savings from reduced administration costs with marstacimab are likely overestimated.

Financial issues:

- The ADAR included cost offsets for reduced breakthrough bleeds in HMB consistent with its cost-utility analysis but not supported by the clinical evidence.
- Consistent with its advice for the economic evaluations, ESC recommended respecifications of the financial estimates for MSAC consideration.
- To manage financial risk from uptake and cost uncertainties, ESC considered a risk share agreement (RSA) with an expenditure cap and large percentage rebate (for use above the cap) is likely unsuitable due to market complexity and multiple competing products. ESC advised that price negotiation, and/or an alternative RSA based on cost per patient and administration costs, would be more appropriate.

ESC Discussion

ESC noted that this application from Pfizer Australia is requesting marstacimab be publicly funded under the National Blood Agreement via listing on the National Product Price List (NPPL), for the treatment of children and adults aged 12 years and over with severe haemophilia A (HMA) or severe haemophilia B (HMB), without inhibitors. ESC noted that marstacimab is registered on the Australian Register of Therapeutic Goods (ARTG) solely for this population and does not have regulatory approval for any other populations (for example, children under the age of 12, patients with inhibitors, or patients with less severe disease).

ESC noted public consultation feedback from one health professional and 4 organisations (Public Pathology Australia, Thrombosis and Haemostasis Society of Australia and New Zealand [THANZ], Haemophilia Foundation Australia and the Australian Haemophilia Centre Directors' Organisation [AHCDO]) that were received prior to the ESC meeting. ESC noted that all feedback regarded marstacimab as a valuable addition, particularly for patients with HMB who lack a subcutaneous treatment option. ESC noted that consumers felt that current management is associated with a significant treatment burden because of the need for frequent administrations. ESC noted from the consultation input that weekly application of a fixed dose using a pen device provides convenience, ease of access and can improve patient quality of life (QoL). ESC noted from the input that there may be a small subpopulation of patients with HMA for whom emicizumab is unsuitable (for example due to side effects or presence of neutralizing antibodies) who may benefit from the proposed intervention. ESC noted that the AHCDO suggested extending the eligibility criteria for marstacimab to patients with moderate HMA or HMB without inhibitors and severe bleeding phenotype, and that patients with HMA or HMB with inhibitors may also benefit. However, ESC noted that marstacimab is not registered on the ARTG for use in these populations. ESC noted that the AHCDO identified no barriers to implementation. ESC considered that there was a need for clinical monitoring of patients and noted from the consultation input that data will be captured through the Australian Bleeding Disorders Registry (ABDR).

ESC noted that the evidence base for marstacimab versus Factor VIII (FVIII) prophylaxis and Factor IX (FIX) prophylaxis consisted of a small, non-randomised, open-label, before-and-after case series of patients with HMA and HMB using self-reported outcomes during 12 months of treatment (BASIS), and an extension of this study with 34.9-month follow-up (BASIS LTE). ESC noted the evidence for emicizumab versus prophylaxis consisted of another small, non-randomised, open-label, before-and-after case series, also using self-reported outcomes

(HAVEN 3). ESC considered that these studies had significant limitations and considered that the evidence included in the ADAR was at high risk of bias.

ESC noted that the BASIS study was undertaken across various countries, and most (73.6%) of the study's population used standard half-life (SHL) factor prophylaxis prior to changing to marstacimab. ESC noted that this does not align with the Australian setting where according to 2021-22 ABDR data, 59.5% of patients with HMA and 80% of patients with HMB use extended half-life (EHL) factor prophylaxis. ESC noted that, in its pre-ESC response, the applicant argued that, in the PSD for MSAC Application 1511, MSAC had considered that there was little clinically important difference between EHL and SHL prophylaxis. However, ESC noted that more recent accumulating observational evidence suggest EHL is superior to SHL, as measured by annualised bleeding rate (ABR) reduction and adherence to treatment. [20,21,22,23] ESC considered that by comparing marstacimab to SHL (the factor prophylaxis used by the majority of patients in BASIS) the incremental effectiveness of marstacimab may be over-estimated compared to the incremental effectiveness that would likely be observed in practice in Australia. 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.

Regarding the comparative effectiveness for people with severe HMA without inhibitors who received prior FVIII prophylaxis, ESC noted that an indirect treatment comparison was used to compare marstacimab (from BASIS) with emicizumab (from HAVEN 3). This comparison did not use a common comparator (i.e. was unanchored) and attempted to adjust for confounders across the studies, including race/ethnicity. ESC considered that it may be more appropriate to adjust for geographic region/country rather than race/ethnicity, to account for differences in healthcare access and management in different countries. ESC also noted that there were significant differences between the studies that introduced substantial concerns regarding the comparison of findings, these are noted below:

- Baseline differences – subjects in BASIS had a higher number of bleeds and a higher number of target joint bleeds than subjects in HAVEN 3.
- Small sample size – the small sample size in each study results in a lack of precision, and the point estimates suggest differences between the populations.
- ABR measure – the ABR measure presented was total bleeds, whereas the primary efficacy outcome of BASIS was treated bleeds.
- Geographical differences – BASIS included a wider range of countries, and there are potential differences in management across countries (such as the percentage use of SHL prophylaxis and other healthcare access differences).
- Temporal differences – the HAVEN 3 data cutoff was in 2017, while enrolment for BASIS started in 2020 and included the COVID-19 period (which may have had impacts on access to healthcare resources resulting in changes to patient management).

[20] 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.
[21] 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
[22] 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
[23] 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 noted the total ABR of 3.58 (95% confidence interval [CI]: 2.37, 5.41) in BASIS (adjusted) compared to 3.3 (95% CI: 2.2, 4.8) in HAVEN 3. ESC also noted that 34% of patients had zero bleeding events in BASIS (adjusted) compared to 44.4% in HAVEN 3. ESC noted that there was no statistically significant difference between these adjusted comparisons. ESC considered that while the results of the indirect comparison appear to support non-inferiority between marstacimab and emicizumab, there is low confidence in these results due to the significant limitations within the studies and the indirect comparison as outlined above.

Regarding the effectiveness of marstacimab compared to factor prophylaxis, ESC noted from the BASIS study that, in the pooled HMA and HMB population, the mean ABR was 7.85 (95% CI: 5.09, 10.61) for factor prophylaxis and 5.08 (95% CI: 3.40, 6.77) for marstacimab. While these results demonstrate a trend towards apparent superior effectiveness of marstacimab compared to factor prophylaxis, ESC noted that fewer patients in the marstacimab arm experienced 0-2 bleeds, and more experienced 3 or more bleeds, compared to the factor prophylaxis arm. Therefore, ESC queried whether mean ABR was the appropriate measure to use, given the disproportionate distribution of patients across each of the bleed categories. ESC noted that the commentary separated the estimated ABR for treated bleeds into HMA and HMB subgroups, in alignment with PASC advice. ESC noted that, although a difference was observed for mean treated ABR between factor prophylaxis and marstacimab, favouring marstacimab in the HMA subgroup (-4.40 ± 13.8 [standard deviation]), no difference was observed when assessing the median treated ABR. Similarly, no difference was observed in the median treated ABR in the HMB subgroup between factor prophylaxis and marstacimab. ESC noted that, if the noninferiority margin nominated in the ADAR (2.5 bleeds/year) is used as the minimum clinically important difference, 44.6% of patients with HMA and 50% of patients with HMB did not experience any clinical important change in the number of treated bleeds after changing to marstacimab. ESC noted that people with HMA were more than twice as likely to have a clinically important reduction in treated bleeds (38.4%), than an increase in treated bleeds (16.9%), after swapping to marstacimab. Furthermore, in the HMB population, 33.3% of patients had clinically important reductions in the rate of bleeds that required treatment and 22.2% had clinically important increases in the number of bleeds that required treatment. ESC noted that the estimates of ABR from BASIS are also substantially higher than have been reported in more recent series of factor prophylaxis.[20]

ESC noted that the pre-ESC response stated that it is appropriate to combine HMA and HMB findings because the mechanism of action of marstacimab is the same for both populations, and that there is no biological reason for a difference in treatment effect. However, ESC considered that apparent differences were observed in the HMA and HMB subgroup analyses presented in the ADAR. For example, ESC noted that the ADAR's forest plot comparing ABRs for treated bleeds by haemophilia type show the mean between-treatment difference for the HMA population was -3.91 (95% CI: -7.10, -0.73), which maintains a noninferiority conclusion for marstacimab versus factor prophylaxis based on treated ABR. However, ESC noted that the upper limit of the 95% CI for the treated ABR in the HMB population does not permit a conclusion of noninferiority based on a noninferiority margin of 2.5 treated bleeds/year (mean treated ABR difference 1.35 [95% CI: -1.44, 4.13]). While ESC acknowledged that these analyses are uncertain due to the small patient numbers, ESC considered that for the purpose of the health technology assessment, these separated estimates for HMA and HMB are informative to both ESC and MSAC.

ESC noted that there were no major differences between marstacimab and factor prophylaxis in terms of QoL measures. However, ESC considered that real-world adherence is likely higher for subcutaneous administration than for intravenous administration[24].

Overall, ESC considered that the results presented in the ADAR support the claim of superior effectiveness over factor prophylaxis for the HMA population, however noted the applicability issues of the BASIS study to the Australian population. ESC considered that the claim of superior effectiveness of marstacimab compared to factor prophylaxis in the HMB population was not supported by the results presented.

ESC noted that etranacogene dezaparvovec (ED), which was supported for funding by MSAC at its July 2025 meeting, is a gene therapy available for the treatment of adult patients with moderately severe or severe HMB (see MSAC Application 1728.1 PSD). ESC agreed with PASC that ED is a relevant near market comparator for the HMB population. ESC noted from the commentary that following infusion of ED, 63% of participants reported no bleeding episodes in months 7 to 18, and 94% of participants were able to cease regular FIX prophylaxis – this corresponds to a lower adjusted ABR (total bleeds) than the rate of treated bleeds reported in BASIS for marstacimab. However, ESC considered these data are highly uncertain, given the naive comparison of two different outcome measures. ESC agreed with the applicant's pre-ESC response that given ED is not yet publicly funded, and because FIX was used as a benchmark for the price of ED, FIX is an appropriate economic comparator for marstacimab. ESC noted another drug, concizumab, is concurrently under consideration by MSAC to treat patients with HMB with or without inhibitors (Application 1805). ESC agreed with PASC that concizumab is a relevant near market comparator but noted that no comparison has been made between marstacimab and concizumab in the current application.

Regarding comparative safety, ESC noted that the crude comparison between HAVEN 3 and BASIS to determine safety against emicizumab did not adjust for differences between the studies. ESC considered that this resulted in low confidence in the findings but considered that most of the reported adverse events were relatively minor in terms of clinical severity. ESC considered the claim of noninferior safety of marstacimab and emicizumab is supported by the results presented, although with low confidence due to the non-adjusted trial differences. For marstacimab versus prophylaxis, ESC noted that while higher rates of adverse events were reported for marstacimab compared to factor prophylaxis, ESC considered the reported adverse events were of relatively minor clinical severity. ESC considered that it was not appropriate to pool the safety outcomes of HMA and HMB and requested the applicant to present the results separated by haemophilia type, in alignment with PASC advice, for MSAC consideration.

ESC noted that for the economic evaluations, the ADAR presented a cost minimisation approach (CMA) for patients with HMA against emicizumab, and a cost-utility analysis (CUA) for a pooled HMA and HMB population with factor prophylaxis as the comparator. ESC noted that the commentary had also presented a CMA for the HMB population against EHL FIX.

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 of 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

[24] Pagnot L, Novais T, Carhoreau V, et al., (2026) Medication adherence after transition to emicizumab in patients with severe hemophilia A: Results from the ADHEMI study, JAPhA Pharmacotherapy, 3(1), 100025

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.

ESC noted that the ADAR's CMA for the HMA population was conducted over the course of one maintenance week. ESC agreed with the commentary that this is not appropriate as marstacimab requires a larger initial loading dose. ESC noted from the commentary that applying the ADAR's parameters over two years resulted in a total cost of $redacted for marstacimab and approximately $1.17 million for emicizumab. ESC agreed with the commentary that a number of model inputs (average body weight, proportion of marstacimab patients receiving dose escalations and adherence to emicizumab) were not appropriate which reduced confidence in the evaluation. ESC noted that the use of the average body weight of patients with HMA and HMB combined (77.8kg) was not appropriate given the average weight of patients with HMA alone was lower (75.2kg). Further to this, ESC noted that the dose escalation of marstacimab used in the model was derived from the BASIS study (4.7%) and agreed with the commentary that a more accurate estimate should be derived from the BASIS LTE study (13.9%) as the observation period was longer. ESC noted that the pre-ESC response defended the use of 4.7% dose escalation in the ADAR, stating it may be an overestimate based on post-marketing data from the UK, Europe and the US showing dose escalations in only 0.5% of patients. However, ESC noted that the results may reflect the use of marstacimab in patients with less severe disease, who are less likely to require a dose escalation. ESC also agreed with the commentary that it is not reasonable to assume perfect treatment compliance for emicizumab and considered that it should align with that used for marstacimab (98%), as both are subcutaneous treatments. ESC considered that these inputs used in the ADAR favoured marstacimab over emicizumab. ESC noted that the ADAR had used the US published prices for emicizumab, and noted the evaluations conducted by the commentary using the effective emicizumab price in Australia in the committee-in-confidence section. ESC requested the CMA for the HMA population be respecified using the appropriate inputs outlined above and the in-confidence emicizumab price for MSAC consideration (see also summary Table 47 below).

For the CMA of the HMB population, ESC noted that the commentary calculated the 2-year total cost for marstacimab as $redacted and for EHL FIX as $377,765. ESC noted that in its base case, the commentary had used similar inputs to the ADAR's CMA against emicizumab (for proportion of dose escalation, and adherence to FIX), to ensure consistency, despite accepting that this resulted in uncertainty. As above, ESC agreed with the commentary that 13.9% (based on BASIS LTE) should be applied for the proportion of dose escalations. ESC advised that the estimate of adherence with EHL FIX should be 87.2% as per published literature.[25] Regarding the administration of EHL FIX, ESC noted that the pre-ESC response had updated the financial analysis by assuming all patients are administered FIX under the guidance of a haematology clinical nurse specialist. ESC noted input from the National Blood Authority that it is likely that a majority of patients self-administer FIX prophylaxis. In alignment with this, ESC noted a Netherlands study which showed that complete self-management of prophylactic treatment was achieved at the age of 23 years.[26] In the absence of published Australian data, ESC advised that

[25] George C, Parikh S, Carter T, Mccosker J, Carlino S, Tran H. 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*. 2023; 29: 1283–1290. https://doi.org/10.1111/hae.14842

[26] Schrijvers, L., Beijlevelt-Van der Zande, M., Peters, M., Lock, J., Cnossen, M., Schuurmans, M., & Fischer, K. (2016). Achieving self-management of prophylactic treatment in adolescents: The case of haemophilia. *Patient education and counseling*, *99*(7), 1179–1183. https://doi.org/10.1016/j.pec.2016.01.016

the administration cost should be a weighted average consisting of 50% self-administration ($0/administration) and 50% under the guidance of a nurse ($375.96/administration; code 40.48 with price weight applied as per National Efficient Price Determination 2025-26), with a sensitivity analysis assessing 100% self-administration. ESC noted that MSAC had previously recommended that there be no price differential across EHL FIX products (MSAC Application 1511 PSD, p. 4), and considered that if there is a difference in the effective prices, the effective price of the lowest priced EHL FIX based on dose should be used in the CMA. ESC noted that to ascertain the EHL FIX dose, the commentary had used the real-world utilisation data from the 2023-24 ABDR provided in the ADAR. ESC noted that a major limitation of this data is that it is not specific to a particular FIX product. ESC considered it more appropriate to use the TGA recommended PI dose for the relevant EHL FIX product. ESC noted that this was the approach the current ADAR had taken for the CMA of emicizumab versus marstacimab. ESC requested the CMA for the HMB population be respecified using the appropriate inputs outlined above and the in-confidence EHL FIX price for MSAC consideration (see also summary Table 47 below).

Table 26: ESC-recommended multiple respecifications for recalculating the CMAs

Variable	Proposed product	Comparator	Rationale
Cost-minimisation approach (CMA) in HMA			
Product cost	*Back-calculated to achieve cost-neutrality* 1. Calculate over 2 years to include loading dose 2. Use 75.2kg body weight 3. Apply 13.9% dose escalation	4. Calculate over 2 years 5. Use 75.2kg body weight 6. Multiply by adherence at 98% 7. Use MSAC recommended in-confidence price of emicizumab	1 to 6: Accept commentary rationale 7: Consistency with in-confidence MSAC recommendation for emicizumab in the requested severe subgroup (PSD for 1579, page 3)
Cost-minimisation approach (CMA) in HMB			
Product cost	*Back-calculated to achieve cost-neutrality* 1. Calculate over 2 years to include loading dose 2. Use 79.2kg body weight 3. Apply 13.9% dose escalation	4. Calculate over 2 years 5. Use 79.2kg body weight 6. Use cheapest EHL FIX in-confidence price based on TGA-approved dose 7. Multiply by adherence at 87.2%	1-5: Accept commentary rationale 6: Consistency with approach in 1805 and MSAC recommendation for no cost differential between EHL FIX products (PSD for 1511, page 4) 7: Observed for FIX[25]
Administration cost	$0	1. Assume 50% patients administered under the guidance of a haematology clinical nurse specialist ($375.96/administration), and 50% of patients self-administer ($0/administration) 2. Adjusted for number of doses administered	1: Input provided by the National Blood Authority and published evidence suggest that a large proportion of patients self-administer. Value for nurse administration ($375.96) obtained from code 40.48 (haematology clinical nurse specialist consult) with price weight applied as per National Efficient Price Determination 2025-26 2: Consistency with product cost and 1728.1 precedent

Regarding the CUA for the HMA and HMB populations presented in the ADAR, ESC noted that the CUA resulted in an incremental cost effectiveness ratio (ICER) per additional QALY gained of $redacted. ESC noted that the inputs used for the key drivers of the ADAR's model, all favoured marstacimab. ESC noted that the pre-ESC response defended the combined CUA for both HMA and HMB populations against FVIII and FIX, on the basis that the mechanism of action of marstacimab is not factor specific. ESC considered that, although the approach of combining

populations may be appropriate to demonstrate overall efficacy for regulatory purposes, it results in low confidence in the estimated extent of incremental (absolute) differences which are subject to treatment effect modifiers. For example, ESC noted the ADAR's approach to adjusting its indirect comparison against emicizumab in HMA. ESC also considered that, in its pre-ESC response, the applicant had misinterpreted PASC's advice to expand the requested population for concizumab (application 1805) to include patients with HMB without inhibitors as well as patients with HMB with inhibitors as being advice to present a combined clinical evaluation across these patient populations.

ESC recalled PASC advice that the economic evaluations for the HMA and HMB populations would need to be separated given that each population has different primary comparators, and that if superiority cannot be demonstrated for the comparison of marstacimab versus EHL FIX prophylaxis, then a CMA would be the most appropriate economic evaluation for the HMB population (as has been presented in the commentary). ESC therefore agreed with the view of the commentary that the presentation of a CUA with pooled HMA and HMB populations was not appropriate because superiority of marstacimab versus EHL FIX has not been established and the main comparator for HMA is emicizumab, not EHL FVIII. In addition, ESC noted that MSAC has not previously accepted any long-term health outcome gains transformed from accepted evidence of reduced rates of bleeds and questioned the strength of the clinical and epidemiological evidence supporting the surrogate to final outcome cascade inferred by the CUA model.

Regarding the financial analysis, ESC noted that the ADAR used epidemiological and market-share approaches to estimate the total number of patients with HMA and HMB who will receive treatment with marstacimab. ESC noted that, based on the ADAR's financial analysis, listing of marstacimab on the NPPL would result in a net cost to the National Blood Agreement of approximately $**redacted** in year 1 increasing to $**redacted** in year 6. It would also result in an overall net cost to the health care system of $23,936 in year 1 increasing to $135,235 in year 6. ESC noted that, although the ADAR's financial estimate only used the population of males aged 12 years and older, the population growth rate was estimated based on the whole Australian population. ESC agreed with the commentary that the population growth rate of males aged 12 years and older should be used in the financial analysis. ESC noted that the ADAR had used implausible patient estimates for prevalent patients with HMA treated with marstacimab, with estimated utilisation reducing in years 4 and 6. ESC considered that this was an artifact of an assumed stepped assumption for the projected switch from FVIII to emicizumab. ESC advised that the financial analysis be respecified to smooth the assumed switch from FVIII to emicizumab. ESC noted that the ADAR assumed that all patients complete a full year of treatment in the year of initiation. ESC noted from the commentary that this does not account for patients commencing treatment at different times during the year, and that due to the small population size, this overestimates the patient years of treatment in the first year by approximately 50%. ESC noted that, in its pre-ESC response, the applicant had inappropriately applied a 50% reduction in the number of patients in the first year (as opposed to number of scripts) to address this issue. ESC considered this issue to be minor as the overestimation in the first year would be largely matched by a corresponding offset from the substitution of the comparator. ESC noted that the ADAR's financial analysis assumed fewer breakthrough bleeds in patients with HMB treated with marstacimab compared to FIX and had therefore included cost offsets associated with treating these bleeds. Given that superior effectiveness of marstacimab against FIX had not been demonstrated, ESC advised that these cost offsets be removed from the financial analysis. ESC advised that the financial analysis be respecified separately for the HMA and HMB populations matching the relevant inputs in the respecified CMA calculations (as outlined above) and the resultant cost-neutral prices. ESC also requested that a weighted average price be calculated for marstacimab across the HMA and HMB populations using the

total costs across the 6-year respecified financial analyses. ESC advice for respecifications for re-calculating the financial analysis are summarised in Table 48 below.

Table 27: Additional ESC-recommended multiple respecifications for recalculating the financial analysis

Variable	Proposed product	Comparator	Rationale
Number of eligible patients with HMA	Smooth the "Remaining prevalent patients with severe HMA treated with marstacimab" for years 1-6 as follows: 85%, 87.5%, 90%, 92.5%, 95%, 97.5%	Accept the consequential change in emicizumab substitutions from this change	The application's projections generate implausible increases and then decreases
Breakthrough bleed costs and offsets	Reject	Reject	For the same reasons as rejecting the CUA (especially not accept superiority shown over FIX in HMB)
Population growth rate	Use population growth rate of males aged ≥ 12 years	Use population growth rate of males aged ≥ 12 years	Given that the ADAR's financial analysis only used the population of males aged 12 years and older, the growth rate pertaining to this population should be used (as opposed to the growth rate of the whole Australian population used in the ADAR).
Per patient per year costs	As for respecified CMAs above, including the back-calculated shadow prices of marstacimab in each population	As for respecified CMAs above	Consistency across economic and financial analyses
Calculate weighted average price across 6 years			

If supported for public funding, ESC considered that there may be a risk of use of marstacimab outside of the TGA registered populations, however noted input from the National Blood Authority that governance measures currently in place have been successful for reducing use in unintended populations for previously funded products. ESC considered that while MSAC has previously advised for risk share agreements with a high rebate for use above an expenditure cap to reduce the risk of unintended usage, ESC considered that this may be challenging to implement for marstacimab because of the complexity of the market (including HMA and HMB therapies) and the number of products. ESC considered a price negotiation to be more appropriate. In addition, MSAC may wish to consider a risk-share agreement based on the total annual marstacimab cost per patient and total administration costs.

ESC requested that the respecified-multivariate analyses of the economic and financial analyses be undertaken prior to MSAC to inform MSAC's consideration. The results of these analyses are reported under Post-ESC work in Section 16. Committee-in-confidence information.

18. Applicant comments on MSAC's Public Summary Document

Pfizer Australia is disappointed with the decision not to recommend funding for people aged 12 years and older with severe HMA and severe HMB, without inhibitors. Patients with severe haemophilia, particularly those with severe HMB, represent a small population. Access to a subcutaneous treatment option could substantially improve quality of life and reduce inequity of access relative to HMA. Pfizer is assessing the possibility of a resubmission in light of evidentiary requirements and expectations of MSAC.

19. Further information on MSAC

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