Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2759

# marstacimab solution for injection in pre-filled pen (Hympavzi®)

## Pfizer Ltd.

05 December 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

**ADVICE**: following a full submission

**marstacimab (Hympavzi®)** is accepted for restricted use within NHSScotland.

**Indication under review**: for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with:

- severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors, or
- severe haemophilia B (congenital factor IX deficiency, FIX < 1%) without factor IX inhibitors.

**SMC restriction**: severe haemophilia B (congenital factor IX deficiency, FIX < 1%) without factor IX inhibitors.

In a one-way, cross-over, open-label phase III study, marstacimab demonstrated superiority in the annualised bleeding rate of treated bleeds compared with routine FVIII or FIX prophylaxis in patients aged at least 12 years with haemophilia A or B who did not have inhibitors.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

**Vice Chair**
**Scottish Medicines Consortium**

# 1. Clinical Context

### 1.1. Medicine background

Marstacimab is a human immunoglobulin G Type 1 (IgG1) monoclonal antibody that targets the Kunitz domain 2 (K2) of tissue factor pathway inhibitor (TFPI); TFPI is the primary inhibitor of the extrinsic coagulation cascade and prevents blood clot formation. Marstacimab binds to and neutralises TFPI, enhances the extrinsic coagulation cascade, and promotes blood clotting.[1, 2]

The recommended dose for patients 12 years of age and older, weighing at least 35 kg, is a loading dose of 300 mg by subcutaneous (SC) injection followed by 150 mg SC once weekly. However, a dose adjustment up to 300 mg SC once weekly can be considered in patients weighing ≥ 50 kg when control of bleeding events is judged to be inadequate by the healthcare professional; the maximum weekly dose of 300 mg should not be exceeded. Marstacimab treatment is intended for long-term prophylactic treatment. See the Summary of Product Characteristics (SPC) for further information.[1]

### 1.2. Disease background

Haemophilia A and B are rare, inherited bleeding disorders caused by partial or complete deficiencies in coagulation Factor VIII (FVIII) or coagulation Factor IX (FIX) respectively; these coagulation factors are crucial for blood clotting. Haemophilia A and B are X-linked recessive inherited disorders that predominantly affects males. Severe haemophilia is defined as having less than 1% of expected clotting factor present.[2, 3]

Prolonged bleeding is the main symptom associated with severe haemophilia A and B, and it usually presents in early childhood with bleeding into the joints and muscles without any injury (spontaneous bleeding).[2, 4] However, life-threatening spontaneous bleeds (for example intracranial or gastrointestinal) can also occur.[3] Recurrent subclinical bleeds into joints cause synovial proliferation and inflammation, which can lead to end-stage degeneration (haemophilic arthropathy). The resulting pain and limited movement can affect patients' ability to participate in daily activities including school or work and sport, and sometimes surgery may be required.[5] Living with severe haemophilia A and B can have a negative impact on well-being and impair quality of life.[2, 3]

In Scotland, there are 837 patients registered as living with haemophilia A and 224 living with haemophilia B, this includes those with less severe forms of the condition.[6]

### 1.3. Company proposed position

The submitting company requested that SMC considered marstacimab in the full population, severe haemophilia A and B. SMC voted to restrict marstacimab for use in the severe haemophilia B population only.

### 1.4. Treatment pathway and relevant comparators

Haemophilia treatment is administered on demand when bleeding occurs or as routine prophylaxis (RP) on a regular basis to prevent bleeds.[3, 4] Severe haemophilia A and B are considered clinically indistinguishable from each other and both are managed mainly with RP.[7] Some people with haemophilia will develop neutralising antibodies, known as inhibitors, against

FVIII and FIX replacement therapies[3]; approximately 7% to 8% of people with severe haemophilia A, and 5% with severe haemophilia B have newly reported or ongoing inhibitors.[6]

Clinical experts consulted by SMC considered that the most common treatment for severe haemophilia A is the monoclonal antibody emicizumab (which is administered by subcutaneous injection).[8] Alternative treatment options include a range of recombinant FVIII replacement products including, for example, turoctocog alfa pegol (Esperoct®) and efmoroctocog alfa (Elocta®).

For severe haemophilia B, the relevant treatments are the recombinant FIX replacement factors. These include, for example, eftrenonacog alfa (Alprolix®), albutrepenonacog alfa (Idelvion®) and nonacog alfa (BeneFIX®).

Factor VIII and IX replacement products are given as intravenous injections which is a substantial treatment burden, extended half-life replacement products are usually favoured over standard half-life products.[3, 4]

Etranacogene dezaparvovec was accepted for use by SMC for severe and moderately severe haemophilia B on an interim basis subject to ongoing evaluation and future reassessment, in August 2024 (SMC2649).

### 1.5. Category for decision-making process

**Eligibility for a PACE meeting**

Marstacimab meets SMC orphan equivalent criteria for this indication.

## 2. Summary of Clinical Evidence

### 2.1. Evidence for the licensed indication under review

Evidence to support the use of marstacimab for this indication comes from the BASIS study. Details are summarised in table 2.1.

**Table 2.1. Overview of relevant studies**

| Criteria | BASIS study[9] |
|---|---|
| Study design | International, one-way, cross-over, open-label phase III study.<br>Note that patients were enrolled into two cohorts based on the presence of inhibitors; the cohorts were then grouped depending on whether they were receiving on demand or RP prior to enrolment. Note that the non-inhibitor cohort who received RP shall only be discussed hereafter as this is the relevant population for the submission. The non-inhibitor cohort of this study is complete. |
| Eligible patients | • Males aged 12 to < 75 years.<br>• Body weight ≥ 35 kg at screening.<br>• Severe haemophilia A (FVIII levels < 1%) or moderately severe to severe haemophilia B (FIX levels ≤ 2%)[a]<br>• Patients enrolled in the 'non-inhibitor cohort' who received RP (n=91) also had the following inclusion criteria:<br>  ○ No detectable or documented history of inhibitors.<br>  ○ Receiving RP prior to enrolment.<br>  ○ Patients on FVIII/FIX RP who have demonstrated at least 80% compliance (determined by the investigator) with scheduled prophylaxis regimen during 6 months prior to |

| | |
|---|---|
| | enrolment and are willing to continue to receive routine prophylaxis treatment with FVIII/FIX replacement during the 6-month observational phase. |
| Treatments | During the 6-month OP, all patients received their current RP factor replacement treatment then during a 12-month ATP, all patients received marstacimab; this was given subcutaneously at a loading dose of 300 mg followed by 150 mg once weekly. Patients weighing ≥ 50 kg who had ≥ 2 spontaneous (atraumatic) bleeds that were treated with infusions of FVIII or FIX were allowed an increased marstacimab dose of 300 mg SC once weekly, any time after 6-months into the ATP. |
| Primary outcome | ABR of treated bleeds, defined as the number of bleeding episodes treated with FVIII or FIX, compared between groups receiving prophylaxis with FVIII or FIX RP (during the 6-month OP) with marstacimab (during the 12-month ATP). |
| Selected Secondary outcomes | Estimated mean ABR for:<br>• Spontaneous bleeds that were treated<br>• Joint bleeds that were treated<br>• Total bleeds that were treated and untreated<br>• Target joint bleeds that were treated<br><br>Treated bleeds = those treated with FVIII or FIX replacement<br>Total bleeds = bleeds treated and not treated with FVIII or FIX replacement<br>Target joint = hip, elbow, wrist, shoulder, knee, and ankle. |
| Statistical analysis | The study protocol specified non-inferiority criterion, with the upper bound of the 95% CI for the difference being: 2.5 for treated bleeds, spontaneous bleeds, and joint bleeds; 1.2 for target joint bleeds; and 2.9 for total bleeds. Non-inferiority was tested for the primary and secondary outcomes in the order specified above; if non-inferiority was met for all of these, superiority was subsequently tested for the primary outcome and established if the confidence interval excluded zero. If the primary outcome was then found to be statistically significant, the HRQoL outcomes were then assessed for non-inferiority (see section 2.2). Efficacy analyses were conducted in the mITT population which consisted of patients who completed the OP and received at least one dose of marstacimab during the ATP.<br><br>Data collected on or after the optional dose escalation (from 150 mg to 300 mg once weekly) following 6 months of marstacimab treatment in the ATP were censored and not included into the primary outcome assessment; this was to avoid over-estimation of the effect of the intended dose. |

ABR = annualised bleeding rate; ATP = active treatment phase; CI = confidence interval; FIX = coagulation factor 9; FVIII = coagulation factor eight; HRQoL = health-related quality of life; mITT = the modified intention-to-treat; OP = observational phase; RP = routine prophylaxis; SC = subcutaneous

[a] In the non-inhibitor cohort, only patients with severe haemophilia B participants were enrolled

At the primary analysis, marstacimab showed non-inferiority and superiority over RP factor-based therapy for the primary outcome, annualised bleeding rate (ABR) of bleeds treated with Factor VIII or IX in the cohort of patients aged at least 12 years with severe haemophilia A or B who did not have inhibitors. The ABR for all selected secondary outcomes were consistently non-inferior to routine prophylaxis.[9] See Table 2.2.

**Table 2.2. Primary and selected secondary outcomes from the BASIS study for the non-inhibitor cohort with routine prophylaxis during the observation phase followed by marstacimab in all patients during the active treatment phase, in the mITT analysis set.[1, 2]**

| | Routine factor-based prophylaxis during the 6-month OP (n=83) | Marstacimab prophylaxis during the 12-month ATP (n=83) |
|---|---|---|
| **Primary outcome: ABR of all bleeds that were treated** | | |
| Estimated Mean ABR (95% CI) | 7.85 (5.09 to 10.61) | 5.08 (3.40 to 6.77) |
| Difference marstacimab versus routine prophylaxis (95% CI), p-value | -2.77 (-5.37 to -0.16) p = 0.038[a] | |
| Patients with zero bleeds, n (%) | 33 (40%) | 29 (35%) |
| Patients with one bleed, n (%) | 9 (11%) | 7 (8.4%) |
| Patients with two bleeds, n (%) | 11 (13%) | 9 (11%) |
| Patients with ≥ 3 bleeds, n (%) | 30 (36%) | 33 (40%) |
| **Secondary outcome: ABR of spontaneous bleeds that were treated** | | |
| Estimated Mean ABR (95% CI) | 5.86 (3.54 to 8.19) | 3.78 (2.25 to 5.31) |
| Difference marstacimab versus routine prophylaxis (95% CI) | -2.09 (-4.23 to 0.06) Non-inferiority met | |
| **Secondary outcome: ABR of joint bleeds that were treated** | | |
| Estimated Mean ABR (95% CI) | 5.66 (3.33 to 7.98) | 4.13 (2.59 to 5.67) |
| Difference marstacimab versus routine prophylaxis (95% CI) | -1.53 (-3.70 to 0.64) Non-inferiority met | |
| **Secondary outcome: ABR of total bleeds that were treated and untreated** | | |
| Estimated Mean ABR (95% CI) | 8.84 (5.97 to 11.72) | 5.97 (4.13 to 7.81) |
| Difference marstacimab versus routine prophylaxis (95% CI) | -2.87 (-5.61, -0.12) Non-inferiority met | |
| **Secondary outcome: ABR of target joint bleeds that were treated** | | |
| Estimated Mean ABR (95% CI) | 3.36 (1.59 to 5.14) | 2.51 (1.25 to 3.76) |
| Difference marstacimab versus routine prophylaxis (95% CI) | -0.86 (-2.41, 0.70) Non-inferiority met | |

ABR = annualised bleeding rate; ATP = active treatment phase; CI = confidence interval; mITT = modified intention-to-treat; OP = observation phase

[a]p-value is for superiority testing.

The estimated mean, difference, and confidence intervals (CIs) for the ABR come from negative binomial regression model.

In the non-inhibitor cohort who had prior RP, 13% (11/83) of patients (5 with haemophilia A and 6 with haemophilia B) had their marstacimab dose increased after 6 months in the ATP, reducing the mean ABR of treated bleeds for these patients from 14.03 to 3.42.[2, 9]

In descriptive subgroup analyses, within the marstacimab 12-month ATP phase and the RP 6-month OP phase respectively, the mean ABR of the primary outcome for patients with: haemophilia A (n=65) was 5.30 compared to 9.16, with a difference of -3.91 (95% confidence

interval [CI]: -7.10 to -0.73); and for those with haemophilia B (n=18) was 4.71 compared to 3.26, with a difference of 1.35 (95% CI: -1.44 to 4.13). The upper bounds of the 95% confidence interval (CI) for the ABR difference among those with haemophilia B (n=18), and adolescent patients (n=17) exceeded the 2.5 non-inferiority margin.[2, 9]

### 2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed in the BASIS study from baseline to 6 months of the OP (RP) and to 6 months of the ATP (marstacimab). This was done using the EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L) index and visual analogue scores; and the Haemophilia Adult Quality of Life (Haem-A-QoL) questionnaire physical health domain and total scores. All four of these scores were secondary outcomes in the statistical testing hierarchy for the prior RP non-inhibitor cohort. Overall, marstacimab demonstrated non-inferiority when compared with prior RP all these scores at 6 months[2, 9]; the EQ-5D-5L data was used in the economic analyses.

Another secondary outcome (not included in the statistical testing hierarchy) included the Haemophilia Joint Health Score (HJHS); this was assessed as the difference in mean changes from baseline at 6 months between the marstacimab prophylaxis in ATP versus the respective reference therapy in OP. The HJHS provides a measure of joint health for the knees, ankles, and elbows. Results at 6 months of the ATP showed comparable results for the prior RP and marstacimab groups.[2]

### 2.3. Supportive studies

Overall, 94% (78/83) of the non-inhibitor cohort (with prior RP) who entered the ATP completed the BASIS study, and 75/78 of these patients continued into the open-label extension (OLE) study (NCT05145127). Patients continued on their marstacimab dose from the end of the BASIS study (150 mg or 300 mg once weekly); safety was the primary outcome for the OLE. At the interim analysis (October 2023 data cut-off), after a median marstacimab treatment duration of 12.5 months (range: 1 to 23 months) beyond the 12-months received in the BASIS study, the mean estimates for the treated and total (treated plus untreated) ABRs were 2.79 (95% CI: 1.95 to 3.98) and 3.17 (95% CI: 2.24 to 4.50) respectively. In those with haemophilia A (n=58) and haemophilia B (n=17) respectively, the mean estimates for the ABRs of treated bleeds were 2.94 (95% CI: 2.01 to 4.31) and 2.24 (95% CI: 0.88 to 5.74).[10] Updated data (combined median marstacimab exposure of 30 months from BASIS and OLE) showed consistent results to the earlier data cut. Compliance with marstacimab was 99%.[11]

### 2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing marstacimab with emicizumab in patients with severe haemophilia A, the submitting company presented an unanchored simulated treatment comparison (STC). The results of the STC informed the economic cost-effectiveness model.

**Table 2.3: Summary of indirect treatment comparison**

| Criteria | Overview |
|---|---|
| Design | Unanchored simulated treatment comparison. |
| Population | Severe haemophilia A without inhibitors, and with prior routine prophylaxis treatment. |
| Comparators | Marstacimab 1.5 mg/kg bodyweight weekly compared with emicizumab 1.5 mg/kg body weight administered weekly. |
| Studies included | BASIS (haemophilia A subgroup)[9] and HAVEN 3 (cohort D).[12] |
| Outcomes | • Mean ABRtotal - incidence of bleeds treated and not treated with FVIII or FIX replacement<br>• Proportion of patients with zero bleeding events (total bleeds) at 6 months<br>• Mean ABRtreat - incidence of bleeds treated with FVIII or FIX replacement<br>• Proportion of patients with zero treated bleeding events (treated bleeds) at 6 months<br>• Mean AJBRtreat - the number of joint bleeds<br><br>Note that rate ratios (RR) for the mean ABR outcomes, and odds ratios (OR) for the proportion outcomes, were used to compare the efficacy of emicizumab and marstacimab and not rate differences. |
| Results | Results for the adjusted STC indicate that there is no clear evidence of a difference between patients treated with marstacimab and emicizumab for any of the five efficacy outcomes. This is consistent across outcomes modelled as RR and OR. |

ABR = annualised bleeding rate; AJBR = annualised joint bleeding rate.

*Other data were also assessed but remain confidential.**

## 3. Summary of Safety Evidence

Evidence from BASIS supports the safety of marstacimab with comparable safety results in those with severe haemophilia A and B.[2]

It should be noted that the BASIS study defined study treatment as marstacimab prophylaxis during ATP; therefore, there were no treatment-related adverse events (AEs) in the OP by design. In BASIS, 23% (19/83) patients had treatment-related AEs including: injection site pruritis (4.8%), pruritis (2.4%), prothrombin fragment 1.2 increased (3.6%), and injection site erythema (3.6%). All other treatment-related AEs were reported in < 2% of patients. All treatment-related AEs were Grade 1 or 2 severity.[2, 9]

Of patients who received marstacimab during the ATP one (1.2%) discontinued their treatment due to an AE (meningioma) that was not related to marstacimab treatment.[2, 9] There were seven patients who experienced ≥ 1 serious AE during the ATP (all in the RP group); 1 event was assessed as treatment-related (grade 1 peripheral swelling).[9] For the 11 patients in the RP cohort who had a marstacimab dose increase during the ATP, no patient experienced a serious AE or an AE that led to discontinuation of marstacimab.[9]

Removal of TFPI inhibition may increase a patient's coagulation potential and contribute to a patient's individual, multifactorial risk for thromboembolic events.[1] No thromboembolic events or severe hypersensitivity or anaphylactic reactions were observed during the BASIS study. However, according to the latest published safety data from the OLE (combined median marstacimab exposure of 30 months from BASIS and OLE), one patient developed deep vein thrombosis, which

was non-life-threatening, did not require hospitalisation, and was treated with anticoagulant therapy.[11]

## 4. Summary of Clinical Effectiveness Considerations

### 4.1. Key strengths

- In the key study, BASIS, marstacimab was superior to routine prophylaxis with FVIII and FIX replacement therapy for the primary outcome of ABR of treated bleeds. These results were considered robust and clinically relevant.[2]
- Secondary outcomes from the BASIS study demonstrated non-inferiority of marstacimab to routine prophylaxis including similar rates of joint bleeds, spontaneous bleeds, target joint bleeds, and total bleeds.[2] Additionally, the results of the HJHS and HRQoL outcomes are supportive.

### 4.2. Key uncertainties

- There are no direct data comparing marstacimab with the most relevant comparator for those with severe haemophilia A, emicizumab. The submitting company provided an unanchored adjusted STC which had several limitations including: differences and limitations in study design, disease severity across studies, treatment duration, the dose of emicizumab was not fully reflective of clinical practice and does not match the economic analysis, substantial differences in the proportion of treated bleeding events across the studies, and no safety or HRQoL outcomes were included. Overall, despite the limitations, the conclusion of similar efficacy between marstacimab and emicizumab seems reasonable.
- The BASIS study results are limited by the non-randomised, open-label design which may introduce several biases to subjective outcomes, including how patients and physicians defined and reported bleeding events.[13] This also limits the relevance of the patient-reported HRQoL outcome results.[2] The length of treatment differed in the observation phase versus the active treatment phase (6 months versus 12 months) which may have impacted the results. In the context of a lifelong chronic condition, there is currently a lack of long-term efficacy and safety data for marstacimab beyond the BASIS and OLE studies where the combined median marstacimab exposure is around 30 months from the latest published data cut-off.[11]
- Results from the descriptive subgroup analysis suggest that the primary outcome (ABR of treated bleeds) was worse in the marstacimab treatment phase compared with routine prophylaxis in patients with haemophilia B. However, the sample size within this subgroup was small (n=18) and the study was not powered to draw statistical conclusions on subgroups. It is noted that the proportion of patients in Scotland with severe haemophilia B is low (approximately 14%)[14], and updated efficacy data from the OLE for these patients are more reassuring.[2]
- The baseline mean ABRs for bleeds that were treated with RP during the OP in BASIS were much higher compared to other clinical studies[2], and likely much higher than would be observed UK clinical practice.[6] This may be due to a group of 15 patients who had a compliance of less than 80% during the RP OP.[2]

- BASIS included different proportions of people having standard half-life and extended half-life RP treatment compared with data from the UK Haemophilia Centre Doctors' Organisation (UKHCDO)[6]; extended half-life products have been associated with lower ABRs in some clinical studies compared with standard half-life products.[3, 15] This, and the compliance issues mentioned earlier, may have resulted in the appearance of more severe disease rather than underlying phenotype.[9]
- Compared with the Scottish population, participants in BASIS were younger, had a lower Body Mass Index (BMI), with a potentially more severe form of haemophilia A, and there were a higher proportion of Asian patients.[14] There is a lack of marstacimab data in older people since the BASIS study excluded patients over 75 years of age, and only one patient was ≥ 65 years of age.[2] It is unclear whether these limitations will affect the generalisability of the study results to the Scottish population.
- The mode of action for marstacimab could increase a patient's overall risk of thromboembolic events.[1, 17] While there has only been one report of a thromboembolic event in the BASIS and OLE studies thus far, the small sample size limited the potential to fully characterise thrombotic events.[9] It was also noted that those with a history of coronary artery disease, venous or arterial thrombosis or ischaemic disease were excluded from the study. A post authorisation safety study is included in the MHRA risk management plan.[18]

### 4.3. Clinical expert input

Clinical experts consulted by SMC considered marstacimab to be a therapeutic advancement due to subcutaneous administration and highlighted that marstacimab would fulfil an unmet need in those with severe haemophilia B (where all currently used treatments are administered intravenously) and severe haemophilia A (as a treatment option for those where emicizumab is unsuitable).

### 4.4. Service implications

Clinical experts consulted by SMC considered that, other than switching the medication and providing self-administration education, there would be minimal service implications.

## 5. Summary of Patient and Carer Involvement

While marstacimab meets SMC orphan equivalent criteria in this indication, the company did not request a Patient and Clinician Engagement (PACE) meeting to consider the added value of marstacimab, in the context of treatments currently available in NHSScotland.

The following information reflects the views of the specified patient group.

- We received a patient group submission from Haemophilia Scotland, which is a Scottish charitable incorporated organisation.
- Haemophilia Scotland has received 30% pharmaceutical company funding in the past two years, with none from the submitting company.
- Despite major advances in treatment, haemophilia continues to place a substantial daily burden on people's lives. Frequent infusions, ongoing pain, mobility issues and the impact on

mental health can all limit independence, education, employment and social participation.

- Treatment still imposes substantial burdens on individuals and families. Managing and administering therapy, particularly intravenous infusions remains time consuming and can be challenging for younger patients and their carers.
- The new treatment's subcutaneous administration removes the need for venous access and helps reduce pain, anxiety and the complexity of treatment. Once weekly dosing would ease treatment fatigue and fit more naturally into people's everyday routines. Its simplicity could also improve adherence.
- For patients with haemophilia B, it would be the first subcutaneous prophylactic treatment marking an important step in equality with those living with haemophilia A in terms of convenience and independence.
- Haemophilia affects the whole family. Carers often share responsibility for treatment and carry the emotional weight of ongoing anxiety about bleeds. A simpler more predictable treatment could help ease this pressure, freeing up time and emotional energy for family life.

# 6. Summary of Comparative Health Economic Evidence

## 6.1. Economic case

**Table 6.1 Description of economic analysis**

| Criteria | Overview |
|---|---|
| Analysis type | Cost utility analysis |
| Time horizon | Lifetime horizon |
| Population | The modelled population included patients aged 12 and above, with documented severe haemophilia (defined as <1% circulating factor level) without factor inhibitors. The model considers two populations, differentiated by haemophilia type (A and B). |
| Comparators | The analysis included three comparators: for haemophilia A the comparators were a basket of FVIII factor replacement treatments and emicizumab; for haemophilia B the comparators were a basket of FIX factor replacement treatments. For the FVIII and FIX basket treatments, market share weights were based on IQVIA (for Pfizer) sales volume data from July 2023 to July 2024.[19] It is assumed that a bleed event is treated with an extra dose of factor prophylaxis FVIII or FIX, depending on haemophilia population, across all treatments' arms. |
| Model description | A Markov model with three health states: bleeds, no bleeds, and death. During each the one-year cycle length, patients in no bleeds experience zero treated bleeds over the year and remain in the same state or they transition to the bleed health state if they experience ≥ 1 bleed in that year. Patients in the bleeds health state accumulate the number and type of bleed event during that year. Death is an absorbing state. This process continues across the lifetime horizon. |
| Clinical data | Clinical inputs were sourced from the BASIS study[9] (12 months for marstacimab; 6 months for FVIII/FIX), with bleed rates and health state distributions derived directly from BASIS. The data also included patients who had a dose escalation of marstacimab. For emicizumab, relative efficacy was informed by an unanchored STC using independent patient data from BASIS and aggregate data from HAVEN 3.[12]<br><br>No adverse events were included in the model. |
| Extrapolation | Bleed rates, efficacy and utilities from the BASIS study are assumed to be constant over the model time horizon, with general population mortality applied in the base case. For emicizumab, odd and rate rations derived from the STC were applied to marstacimabs bleed rates to estimate comparative efficacy. A one-off 6.02% discontinuation rate was applied to marstacimab in the first cycle, and no other discontinuation assumptions were applied to the comparators. |

| | |
|---|---|
| Quality of life | HRQoL data were measured using EQ-5D data. The EQ-5D-5L data reported in the BASIS study reflected the HRQoL of patients experiencing both bleeds and no bleeds, as a single utility value (0.73). The difference between these health states were instead derived from a decrement assigned to acute joint and non-joint bleed events and the difference in disutility for administration method. The disutility decrements (-0.16 and -0.28 for non-joint and joint bleeds respectively) were sourced from literature[20, 21] and assumed to last 4.5 days. The disutility decrements for administration method were sourced from a vignette study.[22] |
| Costs and resource use | Costs included in the model were: medicine acquisition for all treatments and disease management for acute bleed events. |
| PAS | Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. |

FIX = coagulation factor 9; FVIII = coagulation factor 8; HRQoL = Health-related quality of life; STC = simulated treatment comparison

### 6.2. Results

The base case results are presented below. Marstacimab was dominant compared to both FVIII and FIX factor replacement therapies meaning it was estimated as resulting in lower costs and better health outcomes for patients.

The comparison between marstacimab and emicizumab results in a cost-outcome pairing sitting in the South-West quadrant of the cost-effectiveness plane. This means that marstacimab was estimated as resulting in lower total costs and worse health outcomes than emicizumab. When this is the case, a larger ICER indicates higher savings relative to the projected health loss.

**Table 6.2: Base case results for marstacimab versus comparators (with PAS)**

| Population | Comparator | ICER **(£/QALY)** |
|---|---|---|
| **Haemophilia A** | FVIII prophylaxis | Dominant |
| | Emicizumab | SW: £32,892,885 |
| **Haemophilia B** | FIX prophylaxis | Dominant |

FIX = coagulation factor 9; FVIII = coagulation factor 8; ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; SW = south-west; QALYs = quality-adjusted life years.

Key drivers in QALYs comes from the differences in bleed rates between treatment arms thus the differences in disutility decrements being applied and the differences in the administration disutilities. Key driver in costs is medicine acquisition costs.

### 6.3. Sensitivity analyses

Sensitivity analyses included probabilistic, deterministic and scenario analysis. Table 6.3 below illustrated selected scenarios.

**Table 6.3: Selected scenario analysis for marstacimab versa comparators (with PAS)**

| Parameter | | Base case | Scenario | FVIII | Emicizumab | FIX |
|---|---|---|---|---|---|---|
| | | | | ICER (£/QALY) | ICER (£/QALY) | ICER (£/QALY) |
| *Base case* | | | | Dominant | SW: £32,892,885 | Dominant |
| 1 | Starting age | 36 years | Starting age set to the minimum age as per draft SmPC (12 years) | Dominant | CIC | Dominant |
| 2 | Basket comparator composition | IQVIA sales volume data from July 2023 to July 2024 | Factor prophylaxis basket composition informed by UKHCDO 2023 Annual Report[7] | Dominant | CIC | Dominant |
| 3 | Comparative effectiveness | Efficacy data for marstacimab and the two separate basket comparators of FVIII and FIX are informed by BASIS trial data including patients with haemophilia A and haemophilia B | Assume same efficacy across all treatments (regarding occurrence of zero bleed events, ABR and AJBR) | Dominant | CIC | Dominant |
| 4 | | | Assume no patients receive marstacimab dose escalation. Efficacy data for patients with marstacimab dose escalation during the BASIS study ATP excluded in overall $ABR_{treat}$ and AJBR results | Dominant | CIC | Dominant |
| 5 | | | Use BASIS study haemophilia subgroup analysis efficacy data (including dose escalation) | Dominant | CIC | Dominant |
| 6 | | | Use BASIS study haemophilia subgroup analysis efficacy data (excluding dose escalation) | Dominant | CIC | Dominant |
| 7 | | Emicizumab relative efficacy are based on treated bleeds | Emicizumab relative efficacy (odds and rate ratios) are based on total bleed-based analyses | - | CIC | - |
| 8 | discontinuation | a one-off discontinuation rate of 6.02% is applied in the first model cycle for patients | No discontinuation from marstacimab | Dominant | CIC | Dominant |
| 9 | | | Include an annual discontinuation of 6.02% (per year) from marstacimab to factor prophylaxis | Dominant | CIC | Dominant |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | receiving marstacimab | | | | |
| 10 | Adverse events | Excluded | Include | Dominant | CIC | Dominant |
| 11 | Resource use | Included | Assume no resource use per bleed | Dominant | CIC | Dominant |
| 12 | | acute bleed dosing per joint bleed and non-joint bleed are the same | Assume acute bleed dosing per joint bleed is higher than for non-joint bleed | Dominant | CIC | Dominant |
| 13 | | Excluded indirect and direct non-medical costs | Include indirect and direct non-medical costs | Dominant | CIC | Dominant |
| 14 | Disutilities | -0.16 for non-joint, -0.25 for joint bleeds over 4.5 days | Assume non-joint bleeds and joint bleeds have the same disutility per bleed event (−0.28 over 4.5 days) | Dominant | CIC | Dominant |
| 15 | | Included administration based disutilities | Exclude administration based disutilities | Dominant | CIC | Dominant |
| 16 | Mortality | No direct treatment effect on mortality considered | Assume patients with treated bleeds have a SMR of 2.4 (versus the general population) | Dominant | CIC | Dominant |
| 17 | Contract pricing | No contract pricing for comparators | Contract pricing | CIC | CIC | CIC |
| 18 | Time horizon | Lifetime | 2 years | Dominant | CIC | Dominant |

ABR = annualised bleeding rate; AJBR = annualised joint bleeding rate; CIC = commercial in confidence; FIX = coagulation factor 9; FVIII = coagulation factor 8; ICER = incremental cost-effectiveness ratio; LY = life year; NHB = net health benefit; PAS = Patient Access Scheme; QALYs = quality-adjusted life years; SMR = standardised mortality rate; SW = south-west; UKHCDO = United Kingdom Haemophilia Centre Doctors' Organisation

### 6.4. Key strengths

- There was direct evidence available against comparators, FVIII and FIX replacement therapy, from the BASIS study.
- Three types of sensitivity analyses were undertaken: PSA, DSA and scenario analysis
- Appropriate sources were used for valuing treatment acquisition costs.

### 6.5. Key uncertainties

- A key source of uncertainty relates to the duration of available clinical data. Efficacy and bleed rates for marstacimab are derived from 12 months of data from the ATP of the BASIS study, while the factor prophylaxis comparators were informed by 6 months of data from the OP of BASIS. These short-term rates are then assumed to remain constant over the entire time

horizon, with no allowance for treatment waning, disease progression or changes in bleed patterns over time. However, scenario analyses indicate that when alternative efficacy assumptions are applied, scenario 3 in table 6.3, there is limited impact on the cost-effectiveness results. Given the short duration of available evidence and the absence of any long-term dynamics in the model, the use of a lifetime horizon may not add significant value. Scenario 18 in table 6.3 shows no material difference in the overall cost-effectiveness results when the time horizon is reduced to 2 years.

- For comparisons against emicizumab, the model relies on an unanchored STC as there are no direct comparative studies. This approach is inherently uncertain due to the lack of common comparator and any residual differences between the HAVEN 3 and BASIS population could lead to biased estimates of relative bleed rates. In addition, efficacy estimates differ depending on whether treated or total bleeds are used in the analysis, however scenario 7 in table 6.3 shows that this does not lead to a meaningful change in the ICER.
- A key driver of the results is the administrative disutility, which differs between intravenous and subcutaneous administrative methods, and therefore affects the factor prophylaxis arms more heavily. However, scenario 15 in table 6.3 showed no change to the overall cost-effectiveness results when administration disutilities are excluded. Additionally, the model uses a single utility value for both the "bleeds" and "no bleeds" health states, with per bleed disutilities applied additively. This approach does not account for long-term consequences of cumulative joint damage or disease progression. However, if marstacimab does reduce bleed frequency compared with factor prophylaxis, the inclusion of disease progression effects would likely favour marstacimab, making this a relatively conservative modelling assumption.
- The cost of emicizumab, and the FVIII and FIX basket treatments in NHS practice, are lower than the price used in the economic model due to the existence of a national framework agreement for these medicines. Using the national framework contract prices has a substantial upward impact on the cost-effectiveness results in the haemophilia A population in particular.

## 7. Conclusion

The Committee considered the benefits of marstacimab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as marstacimab orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the Committee accepted marstacimab for restricted use in NHSScotland.

## 8. Guidelines and Protocols

In 2020, the British Society of Haematology (BSH) published the Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B.[4]

In 2020, the World Federation of Haemophilia (WFH) published the third edition of their Guidelines for the Management of Haemophilia.[3]

# 9. Additional Information

### 9.1. Product availability date

01 July 2025.

**Table 9.1 List price of medicine under review**

| Medicine | Dose regimen | Cost per year (£) |
|---|---|---|
| **Marstacimab** | **Subcutaneous injection: 300 mg loading dose then a maintenance dose of 150 mg to 300 mg once weekly.*** | **Loading dose: 18,598**<br><br>**Maintenance dose: 483,548 to 967,096** |

**patients weighing ≥ 50 kg who have inadequate control of bleeding events may increase their maintenance dose from 150 mg to 300 mg.*
*Costs from MIMS online and eMC Dictionary of Medicines and Devices Browser on 01 October 2025. Costs do not take any patient access schemes into consideration.*

# 10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 23 patients with severe haemophilia B eligible for treatment with marstacimab in each year, between year 1 and year 3, to which confidential uptake rates were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

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This assessment is based on data submitted by the applicant company up to and including 14 November 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.