Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

# Australian Public Assessment Report for Hympavzi

## Active ingredient: Marstacimab

## Sponsor: Pfizer Australia Pty Ltd

September 2025

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

# About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

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# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ABR | Annualised bleeding rate |
| ADA | Anti-drug antibodies |
| AE | Adverse event |
| aPCC | Activated prothrombin complex concentrate |
| ARTG | Australian Register of Therapeutic Goods |
| ASA | Australia-specific annex |
| AUC | Area under the curve; subscript reflects time period, for example<br>0-168h = from time 0 to 168 hours [1 week]<br>inf = from time 0 to infinity<br>last = from time 0 to time of the last quantifiable concentration |
| BMI | Body mass index |
| $C_{max}$ | Maximum plasma concentration |
| CMI | Consumer Medicines Information |
| DLP | Data lock point |
| ECG | Electrocardiogram |
| HJHS | Haemophilia Joint Health Score |
| IgG | Immunoglobulin G |
| IV | Intravenous |
| mAb | Monoclonal antibody |
| NAb | neutralising antibody |
| PFP | Prefilled pen |
| PFS | Prefilled syringe |
| PI | Product Information |
| PK | Pharmacokinetic |
| PopPK | Population pharmacokinetics |
| PSUR | Periodic safety update report |
| PV | Pharmacovigilance |
| RMP | Risk management plan |
| SAE | Serious adverse effects |
| SC | Subcutaneous |
| TEAE | Treatment-emergent adverse event |
| TFPI | Tissue factor pathway inhibitor |

| Abbreviation | Meaning |
|---|---|
| TGA | Therapeutic Goods Administration |

# Product submission

## Submission details

| | |
|---|---|
| *Type of submission:* | New biological entity |
| *Product name:* | Hympavzi |
| *Active ingredient:* | Marstacimab |
| *Decision:* | Approved |
| *Date of decision:* | 29 January 2025 |
| *Date of entry onto ARTG:* | 29 January 2025 |
| *ARTG number:* | 438990 |
| ▼*Black Triangle Scheme* | Yes |
| *Sponsor's name and address:* | Pfizer Australia Pty Ltd<br>Level 17, 151 Clarence Street<br>Sydney NSW 2000 |
| *Dose form:* | Solution for injection |
| *Strength:* | 150 mg in 1 mL |
| *Container:* | Each carton contains one single-dose prefilled pen. The syringe inside the pen is made from Type I glass with a plunger stopper (chlorobutyl elastomer) and a stainless steel 27 gauge, ½ inch staked needle with a needle shield (thermoplastic elastomer). |
| *Pack size:* | One single-dose prefilled pen |
| *Approved therapeutic use for the current submission:* | Hympavzi is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older with:<br>• severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors, or<br>• severe haemophilia B (congenital factor IX deficiency, FIX < 1%) without factor IX inhibitors. |
| *Route of administration:* | Subcutaneous |
| *Dosage:* | The recommended dose for patients 12 years of age and older, weighing at least 35 kg, is an initial loading dose of 300 mg by subcutaneous injection followed thereafter by 150 mg by subcutaneous injection once weekly.<br>For further information regarding dosage, such as dosage adjustments during treatment, missed doses and switching from prophylactic factor replacement therapy, refer to the Product Information (PI). |
| *Pregnancy category:* | Category D<br>Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal |

malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

# Product background

This AusPAR describes the submission by Pfizer Australia Pty Ltd (the sponsor) to register Hympavzi (marstacimab) for the following proposed indication:[1]

> *Hympavzi is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and paediatric patients 12 years of age and older with:*
> - *haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or*
> - *haemophilia B (congenital factor IX deficiency) without factor IX inhibitors.*

## Conditions

### *Coagulation pathways*

Coagulation is induced in response to injury via the contact activation (intrinsic) pathway and/or the tissue factor (extrinsic) pathway. Factors VIII and IX are activated as part of the intrinsic pathway and contribute through the activation of factor X to factor Xa. Tissue factor pathway inhibitor (TFPI) is an anticoagulant protein that acts on the tissue factor (extrinsic) pathway by inhibiting the effect of factor Xa by its Kunitz-2 domain and inhibiting the effect of factor VII by its Kunitz-1 domain.[2] Marstacimab acts on the Kunitz-2 domain of TFPI, and therefore inhibits TFPI, and preserves the action of factor Xa.

Tissue factor pathway inhibitor is a relatively small polypeptide that has 3 isoforms, all transcribed from the same gene but with alternative mRNA splicing.[3] These 3 isoforms are TFPI−α, TFPI−β, and glycosyl phosphatidyl inositol-anchored TFPI−β. The predominant form in humans is TFPI−α, which is attached to the surface of the endothelium. Tissue factor pathway inhibitor is a Kunitz-type protease inhibitor. It has 3 Kunitz domains, and the Kunitz-2 domain is the target for marstacimab. By inhibiting the Kunitz-2 domain, marstacimab interferes with the function of the factor VIIa-factor Xa complex.

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[2] Mast AE, Ruf W. Regulation of coagulation by tissue factor pathway inhibitor: Implications for hemophilia therapy. *J Thromb Haemost*. 2022 Jun;20(6):1290-1300. doi: 10.1111/jth.15697.

[3] Broze GJ, Girard TJ. Tissue factor pathway inhibitor: structure-function. *Frontiers in Bioscience* 2012; 17: 262-280. doi: 10.2741/3926.

## Haemophilia A

Haemophilia A is an X-linked recessive bleeding disorder caused by a deficiency in the activation of coagulation factor VIII.[4] The condition is caused by mutation on the gene encoding factor VIII, on chromosome Xq28. It can present with variable severity, depending upon the mutation, and the activity of factor VIII. The severity of the mutation depends upon the position of the amino acid within the 3-dimensional structure of the protein, and the potential for partial correction during transcription or ribosomal frameshifting (resulting in production of functional protein). As the condition is X-linked recessive, it is predominantly males who are affected, and inheritance is through the female line.

The severity is classified as:

- mild: levels 3% to 30% of normal; 40% of affected patients
- moderate: levels ≥ 1% to 5% of normal: 10% of affected patients
- severe: levels < 1% of normal: 50% of affected patients.

The clinical signs are due to increased bleeding, with joint and muscles haemorrhages, easy bruising, increased haemorrhage after major surgery or trauma and an increased risk of intracranial haemorrhage. Bleeding into joints (haemarthrosis) leads to joint damage (degenerative arthritis), limitation of motion and permanent disability. Haemorrhage into muscles can lead to muscle necrosis, contractures and peripheral nerve damage (compartment syndrome). Heterozygous female carriers of haemophilia A have concentrations of factor VIII around 50% of normal, and in most cases have decreased coagulability without clinical signs.

In Australia, in the year 2020 to 2021, there were 2621 patients with haemophilia A, which translates to a prevalence of 10.2 per 100,000 population.[5] There were 742 (28.3%) patients with severe phenotype, 248 (9.5%) with moderate, 1441 (55.0%) with mild and 190 (7.2%) unknown. There were 751 (28.7%) patients aged 0 to 19 years, 792 (30.2%) aged 20 to 39 years, 610 (23.3%) aged 40 to 59 years, 403 (15.4%) aged 60 to 79 years and 65 (2.5%) aged ≥ 80 years. There were 1,110 patients who received product for treatment of haemophilia A.

## Haemophilia B

Haemophilia B, also known as Christmas Disease or factor IX deficiency, is phenotypically indistinguishable from haemophilia A. It is an X-linked recessive bleeding disorder caused by a deficiency in the activation of coagulation factor IX.[6] The condition is caused by mutation on the gene encoding factor IX, on chromosome Xq27.1, which is separated from the gene encoding factor VIII by about 50 map units. There are a large number of independent mutations described, each independently leading to haemophilia B.

The severity is classified as:

- mild: levels > 5% to < 40% of normal

[4] Online Mendelian Inheritance in Man (OMIM). #306700 Hemophilia A. https://www.omim.org/entry/306700?search=haemophilia%20A&highlight=%28haemophilia%7Chemophilia%29%20a , accessed 2 February 2024.

[5] Australian Bleeding Disorders Registry (ABDR) Annual Report 2021-22 published by the National Blood Authority. ISSN 1839-0811 (online version) This report is available online at http://www.blood.gov.au/data-analysis-reporting Version: 22 March 2023.

[6] Online Mendelian Inheritance in Man (OMIM). #306900 Hemophilia B. https://www.omim.org/entry/306900?search=Haemophilia%20B&highlight=%28haemophilia%7Chemophilia%29%2Cb , accessed 11 May 2024.

- moderate: levels ≥ 1% to ≤ 5% of normal
- severe: levels < 1% of normal.

In Australia, in the year 2020 to 2021, there were 622 patients with haemophilia B, which translates to a prevalence of 2.5 per 100,000 population.[7] There were 113 (18.2%) patients with severe phenotype, 134 (21.5%) with moderate, 312 (50.2%) with mild and 63 (10.1%) unknown. There were 162 (26.0%) patients aged 0 to 19 years, 180 (28.9%) aged 20 to 39 years, 162 (26.0%) aged 40 to 59 years, 103 (16.6%) aged 60 to 79 years and 15 (2.4%) aged ≥ 80 years. There were 251 patients who received product for treatment of haemophilia B.

## Current treatment options

### *Haemophilia A*

The most commonly used products are recombinant human factor VIII. These can be used prophylactically (either on a regular basis or prior to surgery) or as treatment for a haemorrhage. The frequency of prophylactic treatment depends upon the severity and frequency of bleeding. The aim of prophylactic treatment is to prevent bleeding and joint destruction and to preserve normal musculoskeletal function. Treatment does not reverse established joint damage.

Previously, haemophilia A had been treated with factor VIII concentrates from pooled human serum, obtained from blood donors. This had led to a high rate of transmitted infections, including hepatitis C and AIDS. Hence, the availability of human factor VIII from genetically modified organisms was a major advance. However, human plasma derived products are still available. The Guidelines for Management of Haemophilia in Australia recommend using recombinant products in preference to human plasma derived products.[8]

Patients with haemophilia A who have developed factor VIII inhibitors require alternative treatments. These include recombinant human factor VII and Factor Eight Inhibitor Bypassing Fraction (Feiba).

The blood factor replacement products, including recombinant factor VIII are administered by intravenous infusion. This requires intravenous access, which is commonly provided by indwelling central venous access devices. These devices are prone to obstruction from clots, and to bacterial colonisation. Hence, they have a limited lifespan and require replacement. Intermittent intravenous access can be painful and distressing to the patient, and result in 'needlephobia'.

An alternative treatment is emicizumab. Emicizumab is a humanized bispecific monoclonal antibody that restores the function of missing activated factor VIII by bridging factor IXa and factor X, mimicking activated factor VIIIa independently of factor VIII levels. It can be used in patients with factor VIII inhibitors. It is administered by subcutaneous injection. It can be administered weekly, every 2 weeks or every 4 weeks.

Treatments currently approved in Australia for use in patients with haemophilia A include:

- Biostate, including human coagulation factor VIII, manufactured from New Zealand blood donors, approved in 2000

[7] Australian Bleeding Disorders Registry (ABDR) Annual Report 2021-22 published by the National Blood Authority. ISSN 1839-0811 (online version) This report is available online at http://www.blood.gov.au/data-analysis-reporting Version: 22 March 2023.

[8] Australian Haemophilia Centre Directors' Organisation. Guidelines for Management of Haemophilia in Australia. 2016.

- recombinant human factor VIII
  - Advate (octocog alfa (rch), approved 2005
  - Xyntha (moroctocog alfa [rch], approved 2009
  - Eloctate (efmoroctocog alfa [rhu]), approved 2014
  - Adynovate, (rurioctocog alfa pegol [rch]), approved 2017
- Feiba-NF (factor VIII inhibitor bypassing faction): used in patients who have acquired inhibitors during the course of treatment for haemophilia A. FEIBA results in the generation of Xa and thrombin without the help of the factor VIIIa−IXa complex, thereby bypassing the inhibitory action of factor VIII (or factor IX) inhibitors; approved in 2007
- NovoSeven RT (activated eptacog alfa [bhk]), a recombinant factor VII, used in patients who have acquired inhibitors of factor VIII or factor IX, approved in 2013
- Hemlibra (emicizumab [rch]), approved 2018.

### *Haemophilia B*

The principles of treating haemophilia B are the same as for haemophilia A, but the specific products used differ. The most commonly used products are recombinant human factor IX products. Products used in Australia for treating Haemophilia B include:

- MonoFIX-VF (purified, plasma-derived factor IX), approved 2005
- BeneFIX (nonacog alfa), a recombinant factor IX approved 2007
- Rixubis (nonacog gamma [rch]), approved 2014
- Alprolix (eftrenonacog alfa [rhu]), a long-acting, fully recombinant, fusion protein comprising human coagulation factor IX (FIX) covalently linked to the Fc domain of human IgG1
- NovoSeven RT (activated eptacog alfa [bhk]), a recombinant factor VII, used in patients who have acquired inhibitors of factor VIII or factor IX, approved in 2013

### *TFPI inhibitors*

Concizumab (Alhemo; approved 2023) is an antibody against TFPI that binds to the Kunitz-2 domain of TFPI and inhibits the actions of TFPI. This medicine is approved in Australia for the indication '*Alhemo is indicated where prophylaxis is required to prevent or reduce the frequency of bleeding in patients at least 12 years of age who have haemophilia B (congenital factor IX [FIX] deficiency) with FIX inhibitors, haemophilia A (congenital factor VIII [FVIII] deficiency) and haemophilia A (congenital factor VIII [FVIII] deficiency) with FVIII inhibitors*'.

Befovacimab is a TFPI-inhibitor in development, that had an early termination of a Phase II trial because of thrombotic events.[9] As a result, development has halted.**Error! Bookmark not defined.**

## Clinical rationale

Marstacimab is a human monoclonal IgG1 antibody directed against the Kunitz domain 2 (K2) of TFPI, the primary inhibitor of the extrinsic coagulation cascade. Marstacimab's binding to TFPI

[9] Mancuso ME, Ingham SJM, Kunze M. Befovacimab, an anti-tissue factor pathway inhibitor antibody: Early termination of the multiple-dose, dose-escalating Phase 2 study due to thrombosis. *Haemophilia*. 2022; 28: 702-212.

prevents TFPI's inhibition of factor Xa. Thus, neutralising the activity of TFPI may serve to enhance the extrinsic pathway and bypass the need for replacement factor VIII or factor IX.

# Regulatory status

## Australian regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

## International regulatory status

This submission was evaluated as part of the Australia-Canada-Singapore-Switzerland-United Kingdom (ACCESS) Consortium with work-sharing between the TGA, Health Sciences Authority Singapore and Swissmedic. Each regulator makes independent decisions regarding approval (market authorisation) of the new medicine.

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. The following table summarises these submissions and provides the indications where approved.

**Table 1: International regulatory status**

| Region | Submission date | Status | Approved indications |
|---|---|---|---|
| United States of America | October 2023 | Approved on 11 October 2024 | HYMPAVZI is a tissue factor pathway inhibitor (TFPI) antagonist indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with:<br>Haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or<br>Haemophilia B (congenital factor IX deficiency) without factor IX inhibitors. |

| Region | Submission date | Status | Approved indications |
|---|---|---|---|
| European Union | October 2023 | Approved on 18 November 2024 | Hympavzi is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35kg, with:<br>severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without factor VIII inhibitors, or<br>severe haemophilia B (congenital factor IX deficiency, FIX <1%) without factor IX inhibitors. |
| Switzerland | January 2024 | Approved on 23 December 2024 | Hympavzi is indicated as a routine prophylaxis of bleeding episodes in patients aged 12 years and older weighing at least 35 kg with:<br>severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors, or<br>severe haemophilia B (congenital factor IX deficiency, FIX < 1%) without factor IX inhibitors. |
| Singapore | January 2024 | Under evaluation | |
| United Kingdom | October 2024 | Under evaluation | |
| Canada | October 2023 | Application withdrawn | |

# Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

**Table 2: Timeline for Submission PM-2024-00030-1-6**

| Description | Date |
|---|---|
| Submission dossier accepted and first round evaluation commenced | 1 March 2024 |
| Evaluation completed | 28 October 2024 |

| Description | Date |
|---|---|
| Registration decision (Outcome) | 29 January 2025 |
| Registration in the ARTG completed | 29 January 2025 |
| Number of working days from submission dossier acceptance to registration decision* | 232 days |

*Statutory timeframe for standard submissions is 255 working days

# Assessment overview

Relevant guidelines or guidance documents referred to by the Delegate include:

- Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. EMA/CHMP/BMWP/86289/2010
- Guideline on Reporting the Results of population Pharmacokinetic Analyses. CHMP/EWP/185990/06
- Note for guidance on population exposure: the extent of population exposure to assess clinical safety. CPMP/ICH/375/95.
- Points to consider on application with 1. Meta-analyses; 2. One pivotal study. CPMP/EWP/2330/99.

## Quality evaluation summary

Marstacimab is an IgG1 lambda mAb with 2 identical heavy (H) chains and two identical light (L) chains, covalently linked with 4 inter-chain disulfide bonds. The N-terminus of the L chain is mainly pyroglutamic acid, which is known to spontaneously form in mAbs when the N−terminal residue is Q. The H chain includes 3 alanine substitutions at positions 237, 238, and 240 to minimise the Fc effector functions of the molecule. The N−linked glycosylation consensus sequence, NST, in the CH2 region is essentially fully occupied with asialo, core-fucosylated and complex-type biantennary N-linked glycans with zero, one, and two terminal galactose residues, abbreviated as G0F, G1F, and G2F, respectively. C-terminal K is not encoded by the H chain expression vector cDNA sequence, and therefore the G residue is the H chain C-terminus in marstacimab.

The same formulation composition has been used throughout all clinical studies and commercial production.

The formulation is essentially sodium-free as it contains less than 1 mmol (23 mg) of sodium per 150 mg dose.

The prefilled pen consists of a prefilled syringe, assembled with pen components to form a delivery device.

The quality of this product is acceptable when used in accordance with the conditions defined in the PI, labels, Consumer medicines information (CMI) and the ARTG. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should

have a satisfactory and uniform performance in clinical use. From quality perspective, compliance with therapeutic goods legislation and relevant therapeutic good orders as well as consistency with relevant guidelines and the Australian Regulatory Guidelines for Prescription Medicines has been demonstrated.

# Nonclinical evaluation summary

## General comments

The nonclinical dossier was of high quality and adequate in scope, consistent with the ICH S6 (R1) guideline for biotechnology-derived pharmaceuticals.[10] All pivotal safety-related studies, as well as the tissue cross-reactivity study, were Good Laboratory Practice-compliant.

Marstacimab belongs to the same pharmacological class as concizumab.

The product contains no novel excipients.

## Pharmacology

### Mechanism of action and rationale

Marstacimab is an IgG1 monoclonal antibody directed against the second Kunitz (K2) domain of TFPI. Tissue factor pathway inhibitor is involved in the down-regulation of the initiation of the coagulation cascade through binding to the active site of factor Xa.

Haemophilia A and B patients have normal initiation of the coagulation system but suffer from an inadequate propagation of the coagulation process due to deficiency in factor VIII or factor IX, leading to impaired factor Xa generation and, consequently, impaired fibrin clot formation.

By binding to TFPI, marstacimab is intended to reduce TFPI inhibitory activity so that the factor Xa produced by the factor VIIa/tissue factor complex will result in sufficient generation of thrombin to achieve haemostasis.

### Primary pharmacology

In vitro, marstacimab was shown to bind to human TFPI with nanomolar affinity ($K_D$, 3.7 nM), targeting the K2 domain and not the K1 domain. Marstacimab also recognises the mouse, rat, rabbit and cynomolgus monkey forms of TFPI, displaying higher (2.4 to 6.4-fold) or comparable affinity cf. for human TFPI. Marstacimab neutralised human TFPI to increase factor Xa activity (half maximal effect concentration ($EC_{50}$), 8.75 nM), enhanced thrombin generation and shortened dilute prothrombin time in human plasma (nonhaemophilic and haemophilic A and B), and decreased clotting time and clot formation time in normal human whole blood.

In vivo, marstacimab reduced blood loss induced by injury in mouse models of haemophilia A and haemophilia B when administered intravenously (IV) prior to induction of bleeding; protection was long lasting (at least 72–189 h after a single 6 mg/kg dose). Restoration of haemostasis was also shown with administration post-injury. Decreased dilute prothrombin time was shown in plasma from cynomolgus monkeys treated with marstacimab subcutaneously (SC) or IV.

[10] ICH guideline S6 (R1) - preclinical safety evaluation of biotechnology-derived pharmaceuticals | Therapeutic Goods Administration (TGA)

### Secondary pharmacodynamics and cross reactivity

The Fc region of marstacimab contains mutations introduced to reduce effector function. Marstacimab (≤ 30 µg/mL) displayed no binding to C1q or FcγR, supporting a low potential for induction of complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity.

Immunohistochemical studies using a suitably comprehensive panel of human (as well as cynomolgus monkey and rat) tissues revealed a binding pattern consistent with the known expression of TFPI (for example, vascular endothelial cells, fibroblasts, mononuclear cells and spindle cells) for the most part. Where binding was observed in sites not known to express TFPI, this was localised to the cytoplasm (largely inaccessible to marstacimab in vivo). Accordingly, no toxicologically relevant off-target binding by marstacimab is identified.

### Pharmacodynamic drug interactions

The pharmacodynamic (PD) effect of marstacimab in combination with eptacog alfa (NovoSeven), activated prothrombin complex concentrate (aPCC; factor VIII inhibitor bypassing fraction; Feiba) or factor VIIa + factor X in a 1:10 ratio (Byclot) was examined in vitro (in platelet-poor human haemophilic A and B plasma [mostly with inhibitors]) and in vivo (in rats).

- Combination of marstacimab with NovoSeven resulted in only a minimal increase in thrombin generation cf. that obtained with marstacimab alone in plasma in vitro; peak thrombin levels did not exceed the level observed in non-haemophilic plasma with marstacimab alone.
- Combination of marstacimab with Feiba enhanced thrombin generation cf. either single agent in vitro, with peak thrombin concentrations within the range in studies reported for normal non-haemophilic plasma.
- A similar additive effect as seen with Feiba was found for marstacimab in combination with Byclot in vitro.
- An increase in the incidence/severity of thrombi/emboli (pharmacologically mediated) cf. that with the single agents was seen with marstacimab in combination with NovoSeven in rats; the combination produced no significant additional reduction in prothrombin time.
- Marstacimab and Feiba co-treatment in rats led to an increase in mean thrombin-antithrombin complexes (an indicator of thrombin generation) and mean platelet volume cf. that with Feiba alone; reductions in prothrombin time with the combination were comparable to that with single-agent Feiba.
- Combined treatment with marstacimab and Byclot in rats produced similar effects on coagulation parameters cf. that observed with Byclot alone.

### Safety pharmacology

Examination of safety pharmacology endpoints was incorporated into the 13-week repeat-dose toxicity study in cynomolgus monkeys. No effects on neurobehavioral parameters, electrocardiogram (ECG), heart rate, blood pressure or respiratory rate were observed with marstacimab up to the highest doses tested (90 mg/kg/week SC and 500 mg/kg/week IV), yielding plasma concentrations at least 33 times higher than the maximum plasma concentration ($C_{max}$) in patients at the maximum recommended clinical dose of 300 mg SC once weekly [= 75.2 µg/mL].

### Pharmacokinetics

Marstacimab displayed a pharmacokinetic (PK) profile typical of a monoclonal antibody in laboratory animal species and humans, characterised by a long plasma half-life and low volume of distribution (consistent with limited distribution outside the vascular compartment). Target-mediated drug disposition was evident. Bioavailability by the SC route in rats was approximately 70%, similar to humans. No studies on tissue distribution, metabolism, excretion or enzyme/transporter interactions were included in the submission; this is acceptable for a protein drug. Marstacimab exposure was seen to be unaffected by co-treatment with NovoSeven, Feiba or Byclot; and NovoSeven exposure unaffected by marstacimab in pharmacology studies in rats.

## Toxicity

### Acute toxicity

Single-dose toxicity studies were not conducted. A low order of acute toxicity is seen for marstacimab from findings in the repeat-dose toxicity program, with no treatment-related mortality or adverse clinical signs encountered up to the highest doses tested (180 mg/kg/week SC and 1000 mg/kg/week IV in rats, and 90 mg/kg/week SC and 500 mg/kg/week IV in monkeys).

### Repeat-dose toxicity

Key repeat-dose toxicity studies comprised 3- and 6-month studies in rats and a 3-month study in cynomolgus monkeys; 8-day pilot studies were also performed in the 2 species. All involved once-weekly SC and/or IV administration. The pivotal studies were appropriately designed and conducted in terms of dose selection, duration, group size and range of endpoints examined. Findings by the IV route in animals can be applied to SC administration in patients, bridged by toxicokinetic data.

### Relative exposure

Exposure ratios achieved in the key repeat-dose toxicity studies have been calculated based on plasma $AUC_{0-168\,h}$. The human reference AUC value used is for the maximum recommended clinical dose of 300 mg/week in adolescents. Very high multiples of the maximum anticipated human exposure were obtained at the highest dose levels tested in rats and monkeys.

Anti-drug antibodies (ADA) developed in treated rats, without affecting exposure or abolishing pharmacological activity. Anti-drug antibodies were not observed in monkeys. Immunogenicity in animals is of low predictive value for humans.

### Major findings

Marstacimab was well tolerated. Key findings in the repeat-dose toxicity program were:

- effects on the coagulation cascade (including altered prothrombin time, decreased serum fibrinogen and increased D-dimer [= fibrinolytic by-product] concentration [seen across species and studies])
- thrombi/emboli in the lung and IV injection site (tail vein) [rats only; minimal grade].

These were not regarded as adverse based on magnitude/severity, and represent exaggerated pharmacological effects in animals with a normal coagulation system. Treatment-related microscopic changes with marstacimab were confined to rats, with none observed in monkeys. The pivotal studies establish no-observed-adverse-effect levels (NOAELs) of 1000 mg/kg/week

IV in rats, and 90 mg/kg/week SC and 500 mg/kg/week IV in monkeys (relative exposure, 30 to 165).

### Genotoxicity

No genotoxicity studies were submitted. This is acceptable, and in accordance with ICH S6 (R1). As a large protein molecule, marstacimab is not expected to interact directly with DNA or other chromosomal material.

### Carcinogenicity

No carcinogenicity studies were submitted. In line with ICH S6 (R1), carcinogenic potential was considered from the mode of action of the drug and the physiological role of the target based on a review of the scientific literature, and from findings in the general toxicity program. No cause for concern for increased/enhanced tumour development in patients treated with marstacimab is seen.

### Reproductive and developmental toxicity

Reproductive and developmental toxicity studies with marstacimab covered male fertility only. The absence of studies on female fertility, early embryonic development (in treated females), embryofetal development and pre- and postnatal development is acceptable, justified by the indicated patient population (which is almost exclusively male). The male fertility study was appropriately designed and conducted in terms of number of animals, species selection, dose selection and the timing/duration of treatment.

Fertility was unaffected in male rats up to the highest dose tested (≤ 1000 mg/kg/week IV; estimated relative exposure above 150 [from toxicokinetic data obtained in the general repeat-dose toxicity studies]). No treatment-related histopathological changes in the male or female reproductive tract to suggest potential impairment of fertility were observed in the general repeat-dose toxicity program.

Published knockout studies identify TFPI as critical for development, with inactivation of the TFPI gene in mice shown to result in embryofetal lethality.[11,12] As an IgG antibody, placental transfer of marstacimab is expected, increasing in a linear fashion as pregnancy progresses.

### Pregnancy classification

The sponsor has proposed Pregnancy Category B2. Given concerns for potential embryofetal lethality seen from the mode of action, assignment to Pregnancy Category D is warranted instead. Category D is also better aligned with the sponsor's recommendation for the use of contraception in women of childbearing potential, and matches the existing category for concizumab.

### Immunotoxicity

Marstacimab (≤ 1000 µg/mL) did not induce cytokine release in human whole blood in vitro.

### Local tolerance

A dedicated study in rats established good local tolerance of marstacimab following SC injection at the proposed clinical strength (150 mg/mL). Injection site findings were minor and not

[11] Ellery PE, Maroney SA, Cooley BC, et al. A balance between TFPI and thrombin-mediated platelet activation is required for murine embryonic development. *Blood* 2015; 125(26):4078-84. doi: 10.1182/blood-2015-03-633958

[12] Huang ZF, Higuchi D, Lasky N, Broze GJ. Tissue factor pathway inhibitor gene disruption produces intrauterine lethality in mice. *Blood* 1997; 90(3):944-51. doi: 10.1182/blood.V90.3.944

toxicologically significant, comprising minimal to mild mixed cell infiltration that was often associated with minimal oedema and/or haemorrhage. Good local tolerance was also evident from the general repeat-dose toxicity program, but the highest tested strengths in those studies (18 mg/mL SC and 100 mg/mL IV) were well below the strength proposed for administration to patients.

### *Comments on the Nonclinical Safety Specification of the Risk Management Plan*

Key safety concerns raised by the nonclinical program for marstacimab are mostly adequately identified in the draft Risk Management Plan. While, as the sponsor states, no hazard for embryofetal development was identified (as no such study was performed), concerns for potential harm are held based on the drug's mode of action (that is, its pharmacological target is recognised to be critical to development). Revision of the Pregnancy Category and Use in pregnancy statement in the Product Information will serve as an appropriate risk mitigation strategy.

## Conclusions and recommendation

The nonclinical dossier contained no major deficiencies.

The submitted primary pharmacology studies offer support for the utility of marstacimab for the proposed indications.

The key concerns for patients identified from nonclinical data are:

- thromboembolic events at high doses
- embryofetal lethality if used during pregnancy.

Marstacimab should be assigned to Pregnancy Category D, rather than Category B2 as the sponsor proposes.

There is no nonclinical objection to registration of Hympavzi for the proposed indications.

# Clinical evaluation summary

## Summary of clinical studies

The clinical dossier consisted of:

- four Phase I/II studies
- one Phase III study (pivotal study)
- two other efficacy studies, including a follow-on extension study of the pivotal study
- two population pharmacokinetic (PopPK) studies.

The dossier includes data for adults and adolescents aged 12 to 17 years.

There is an agreed Paediatric Investigation Plan in Europe. There is a waiver in the US for a Paediatric Assessment on the following grounds:

> Marstacimab received Orphan Designation and is therefore exempt from PREA requirements, however, Pfizer has proactively submitted an initial Pediatric Study Plan and it was agreed with the FDA in September 2021. As agreed in the Type B meeting 21 June 2023, the initial Pediatric Study Plan is provided in the BLA and an assessment is not needed.

The clinical evaluation commented:

> For several of the clinical studies the submitted reports were interim reports. (NOTE sponsor amendment – 'For two of the clinical studies (B7841005 & B7841007) the submitted reports were interim reports, although for B7841005 the sponsor clarified that the data and documentation provided are that of a final, completed study in the population strata of individuals without inhibitors'.) These reports did not include complete descriptions of the statistical methods and instead provided links to the study protocols. However, the study protocols were also incomplete, particularly in the description of the non-inferiority analyses. Hence, in the opinion of the Clinical Evaluator, given that the non-inferiority analysis is key to the interpretation of the results, this should have been explained in the study report.
>
> However, the population pharmacokinetic studies were conducted to a high standard and were reported satisfactorily.

# Pharmacology

## *Pharmacokinetics*

**Table 3: Pharmacokinetic studies**

| PK topic | Subtopic | Study ID |
|---|---|---|
| PK in healthy adults | General PK - Single dose | Study B7841001 |
| | Bioequivalence * - Single dose | Study B7841009 |
| PK in haemophilia patients | General PK - Single dose | Study B7841010 |
| | General PK - Multi-dose | Study B7841002 |
| Population PK analyses | Target population | PMAR-EQDD-B784a-DP3-1021 |
| | | PMAR-EQDD-B784a-DP3-1331 |

* Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

### *Absorption*

In Study B7841010 following SC administration the absorption of marstacimab appears to be first order. For a 300 mg single dose administered SC, the geometric mean (CV%) for $C_{max}$ was 15,610 ng/mL (35%), for $AUC_{last}$ was 2,917,000 ng•hr/mL (60%) and $AUC_{inf}$ was 4,549,000 ng•hr/mL (7%). Median (range) time of occurrence of maximum observed concentration was 73.15 (71.9 to 167) hours.

### *Bioavailability*

In Study B7841001, following single dose administration to healthy volunteers, the SC and IV routes were not bioequivalent: the ratio (90% CI) of adjusted means of SC to IV was 27.31% (20.04 to 37.23%).

In PopPK analysis PMAR-EQDD-B784a-DP3-Amendment bioavailability was estimated as 70.5%.

In Study B7841001, the steady-state volume of distribution ($V_{ss}$) following IV dosing ranged from 3.525 L to 3.880 L.

In Study B7841010, following SC administration of a 300 mg dose, the apparent volume of distribution was 8.305 L (29%).

### Sites of metabolism and mechanisms / enzyme systems involved

The sponsor states in the PI:

> Similar to other therapeutic proteins with molecular weights above the glomerular filtration cut-off, marstacimab is expected to undergo proteolytic catabolism and receptor-mediated clearance. In addition, based on the [target mediated drug disposition] TMDD, marstacimab is expected to be also cleared by target-mediated clearance as formation of marstacimab/TFPI complex.

This statement is consistent with the PK and PK-PD data.

### Routes and mechanisms of excretion

As a mAb, marstacimab is expected to be cleared by catabolism following endocytosis by the mononuclear phagocytic system. This would be expected to extend also to the marstacimab-TFPI complex.

In Study B7841001 clearance decreased with increasing dose, and exposure to marstacimab was not dose-proportional. The plasma concentration time profiles suggest a one-compartment model, with decreased clearance at higher doses. Half-life ranged from 33.3 hours for the 100 mg SC dose in non-Japanese subjects to 98.35 hours for the 300 mg SC dose in Japanese subjects.

In Study B7841010 following SC administration of a 300 mg dose, the geometric mean (CV%) for clearance/bioavailability was 0.06595 L/hr (7%). The arithmetic mean (SD) $t_{½}$ was 90.48 (26.025) hours.

In Study B7841002 steady state was reached after the fifth dose or week on treatment. The minimum and maximum plasma concentrations ($C_{min}$ and $C_{max}$) reflected the dose sizes, but clearance/bioavailability was similar for all the dose regimens. Overall, mean (CV%)] clearance/bioavailability at 300 mg SC once weekly (Inhibitors and Non-Inhibitors combined) was 32.79 mL/hour (41%).

## Population pharmacokinetics (Pop PK)

### PopPK analysis PMAR-EQDD-B784a-DP3-1021

PopPK analysis PMAR-EQDD-B784a-DP3-1021 was a population PK and PD modelling of marstacimab. The study analysed data from Study B7841001 in healthy volunteers and Study B7841002 in subjects with haemophilia. The base model used a target mediated drug disposition (TMDD) model. The final model was a TMDD model with quasi-steady state approximation with a non-linear clearance for both total drug and the drug-target complex. Weight was retained as a covariate on clearance and intercompartmental clearance with an allometric exponent of 0.75, and on central volume of distribution and peripheral volume of distribution with an allometric exponent of 1.

The parameters were estimated with acceptable precision. The typical values (RSE%) were 2.78 (11.2%) L for central volume of distribution, 2.71 (17.5%) for peripheral volume of distribution, and 0.00871(23.5%) L/h for clearance.

### PopPK analysis PMAR-EQDD-B784a-DP3-1331-Amendment

PopPK analysis PMAR-EQDD-B784a-DP3-1331-Amendment was a population PK and PK-PD analysis that was conducted using data from healthy adult participants as well as adult (≥ 18 years of age) and adolescent (12 to < 18 years of age) participants with haemophilia in the Phase I, II and III studies to characterise marstacimab PK and total TFPI concentrations and their effect on the key biomarker peak thrombin. The study was used a confirmatory study of the previously developed PK-PD model and the dosing regimen used in the Phase III study.

The data were obtained from six studies:

- Study B7841001 conducted in healthy volunteers
- Study B7841009 conducted in healthy volunteers
- Study B7841002 conducted in subjects with haemophilia
- Study B7841003 conducted in subjects with haemophilia
- Study B7841005 conducted in subjects with haemophilia
- Study B7841010 conducted in Chinese subjects with haemophilia.

The final model included the following additional covariate effects, in addition to body weight:

- Additional effect on clearance for Healthy Population
- Additional effect on clearance for Asian subjects
- Additional effect on clearance for ADA positive subjects
- Additional effect on clearance for Mild-renal impairment
- Additional effect on clearance for Haemophilia B subjects.

Anti-drug antibody positive status was estimated to result in 22.9% increase in CL, the corresponding change in clearance due to mild renal impairment (creatinine clearance (CRCL) < 90 mL/min/$m^2$) and in haemophilia B participants was estimated to be a 16.85% decrease and 11.8% decrease respectively. These were not considered to be clinically significant. In addition, there was no clinically significant difference in PK between adults and adolescents, or based on race or patient type.

The typical estimates (RSE%) were 3.61 (9.2%) L for central volume of distribution, 0.0188 (11.3%) L/h for clearance and 4.99 (10.5%) L for peripheral volume of distribution.

The pharmacokinetics of marstacimab have been adequately characterised.

Marstacimab has complex pharmacokinetics, primarily because of target mediated disposition. The target mediated disposition does not appear to be saturated at the concentrations expected from 150 mg once weekly and 300 mg once weekly administration. This is because the nonlinear kinetics are apparent in this concentration range. Typically, with a monoclonal antibody, the target mediated disposition is saturated at lower doses, and the nonlinear kinetics are not apparent at higher doses. However, for marstacimab the interindividual and intraindividual variability are acceptable and the plasma concentrations are predictable.

The clearance of marstacimab is higher than is typical for a monoclonal antibody. This is because the disposition is primarily target mediated at the concentrations expected from the proposed dosing regimen. In comparison, the clearance of monoclonal antibodies is typically due primarily to catabolism in the lymphoreticular system. Hence the dosing is more frequent (at once weekly) for marstacimab than for a typical monoclonal antibody drug product.

The sponsor has demonstrated the prefilled syringe (PFS) and prefilled pen (PFP) are bioequivalent, and therefore interchangeable.

## *Pharmacodynamics*

The pharmacodynamics (PD) of marstacimab have been adequately characterised.

The thrombin generation assay provides a picture of the status of thrombin generation and inhibition.[13] It is a marker of coagulation activity. Peak thrombin activity measures the maximum amount of thrombin generated during the test. Hence, these tests measure the ability of the coagulation system to respond to clotting stimuli.

Prothrombin fragments 1+2 is a marker of coagulation activation and has a high sensitivity and specificity for thrombosis, specifically for thrombin generation.[14] It is released from prothrombin by the catalytic action of the prothrombinase complex. D-dimer is formed from the D-units of platelets, and are broken from the platelets as a clot breaks down.[15] Hence, prothrombin fragments 1+2 indicate clot formation and D-dimer indicates clot degradation.

Hence, the PD data indicate that following marstacimab administration, there is an increase in the ability to generate clots and increase in thrombosis, followed by an increase in clot degradation. Overall, the coagulation system is stimulated.

The effect appears to be significantly greater in healthy subjects compared to subjects with haemophilia. Peak thrombin in healthy subjects was double the value for subjects with haemophilia.

The conclusion of the clinical evaluation was that the PK data and the PK-PD data support the proposed dosing regimen.

# Efficacy

## *Study B7841005*

This was an open-label, one-way crossover study to demonstrate efficacy and safety of marstacimab in adolescents and adults with severe haemophilia A or moderately severe to severe haemophilia B, with or without inhibitors. The study was conducted at 52 sites in 19 countries. The study commenced on 9 March 2020 and an interim report was provided for the period up to 17 April 2023.

Inclusion criteria were males 12-75yrs of age with a diagnosis of severe haemophilia A or B (factor VIII or factor IX activity less than ≤ 2%, respectively). There were different criteria for the Non-Inhibitor Cohort versus the Inhibitor cohort.

The study treatments were:

- Marstacimab 300 mg loading dose, followed by 150 mg once weekly. Participants who met the dose escalation criteria could have the dose increased to 300 mg once weekly. The dose escalation criteria were:
  - Non-Inhibitor Cohort: Two or more spontaneous (atraumatic) bleeds (consisting of joint bleeds and/or significant soft tissue/muscle or other site bleeds) treated with infusion(s) of coagulation factor VIII or factor IX over a 6-month period in the absence of a confirmed factor VIII or factor IX inhibitor, respectively.

[13] Depasse F, Binder NB, Mueller J, Wissel T, Schwers S, Germer M, et al. Thrombin generation assays are versatile tools in blood coagulation analysis: A review of technical features, and applications from research to laboratory routine. *J Thromb Haemost*. 2021;19(12):2907-2917. doi: 10.1111/jth.15529.

[14] Al-Samkari H, Song F, Van Cott EM, Kuter DJ, Rosovsky R. Evaluation of the prothrombin fragment 1.2 in patients with coronavirus disease 2019 (COVID-19). *Am J Hematol*. 2020;95(12):1479-1485. doi: 10.1002/ajh.25962.

[15] Killeen RB, Kok SJ. D-Dimer Test. [Updated 2025 Jun 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431064/

– Inhibitor Cohort: Two or more spontaneous (atraumatic) bleeds (consisting of joint bleeds and/or significant soft tissue/muscle or other site bleeds) treated with infusion(s) of NovoSeven over a 6-month period.

The study treatment was provided as a PFS. Multiple injections were to use a unique site for each injection.

Following completion of the observation phase, participants were required to adhere to a required washout period from their haemostatic products as follows:

- from factor VIII replacement therapy for at least 72 hours
- from extended half-life factor VIII replacement therapy for at least 4 half-lives
- from factor IX replacement therapy for at least 96 hours
- from extended half-life factor IX replacement therapy for at 4 half-lives
- from bypass agent therapy from either recombinant factor VIIa or activated prothrombin complex concentrate (aPCC) for at least 72 hours.

The permitted treatments for breakthrough bleeding were:

- subjects without inhibitor: factor VIII or factor IX at minimum effective dose as per label
- subjects with inhibitor: recombinant factor VIIa (≤ 90 μg/kg approximately every 2 hours) or aPCC

The prohibited medications included immunomodulatory agents, systemic antifibrinolytic agents and medications known to affect platelet function.

The primary efficacy outcome measure was the annualised bleeding rate (ABR). The secondary efficacy outcome measures were:

- incidence of joint bleeds
- incidence of spontaneous bleeds
- incidence of target joint bleeds
- incidence of total bleeds (treated and untreated)
- change from baseline in Haemophilia Joint Health Score (HJHS)

The patient reported outcome measures were:

- Haemophilia Quality of Life Questionnaire for Adults/Haemophilia Quality of Life Questionnaire for Children (Haem-A-QoL/Haemo-QoL)
- Haemophilia Activities List (HAL/pedHAL)
- EuroQol 5 Dimensions 5 Level (EQ-5D-5L)
- Patient Global Impression of Change – Haemophilia (PGIC-H).

The primary efficacy outcome measure was tested using the 95% CI for the ratio of ABR prophylaxis/demand (that is, marstacimab/observational) for non-inhibitor cohort with on-demand treatment. Superiority for the non-inhibitor, prior on-demand group was demonstrated if the 95% CI were below the pre-set threshold of 0.5. The primary efficacy outcome measure was tested using the 95% CI for the difference of ABR prophylaxis versus routine factor prophylaxis (that is, marstacimab - observational) for non-inhibitor cohort with routine

prophylaxis treatment. Non-inferiority for was demonstrated if the 95% CI were below the pre-set threshold of 2.5.

### Results for the primary efficacy outcome

*Non-inhibitor, on-demand group: test for superiority*

For the non-inhibitor, on-demand group, the mean (95% CI) model based estimate for ABR during the observation period was 38.00 (31.03 to 46.54) /year and during the active treatment phase was 3.18 (2.09 to 4.85) /year; ratio estimate (95% CI) 0.084 (0.059 to 0.119) $p < 0.001$. Efficacy was demonstrated for haemophilia A [ratio estimate (95% CI) 0.0894 (0.062 to 0.130)] and haemophilia B [ratio estimate (95% CI) 0.036 (0.012 to 0.111)]. There were insufficient subjects to test for efficacy separately in adolescents.

*Non-inhibitor, prior prophylaxis group: test for non-inferiority*

For the non-inhibitor, prophylaxis group, the mean (95% CI) model based estimate for ABR during the observation period was 7.85 (5.09 to 10.61) /year and during the active treatment phase was 5.08 (3.40 to 6.77) /year; rate difference (95% CI) −2.77 (−5.37 to −0.16), non-inferiority criterion was the upper bound of 95% CI less than 2.5. In the subgroup analysis, non-inferiority was not demonstrated separately for haemophilia B or for adolescents.

### Evaluation commentary

The study population is similar to the target population in Australia. The inclusion criteria were not overly restrictive, and do not limit the generalisability of the results. The study treatment was administered at the same dose, and in the same way, as the dosing and administration advice in the PI. However, the study did not use the PFP, but instead only used the PFS.

The outcome measures were clinically relevant and reflected measures used in clinical practice to guide and monitor treatment. The outcome measures were objective and had sufficient sensitivity to demonstrate a change with treatment.

The study was not blinded and was sequential; i.e. the observation phase occurred before the active treatment phase. However, the primary outcome measure was objective and not open to measurement bias. The effect size for the on-demand group was large, and unlikely to have occurred due to disease progression or changes in study personnel. A placebo-controlled trial might also have been unblinded due to investigations. Hence, the Clinical Evaluator considers the study design to be acceptable.

The interim results of the study demonstrated superiority for marstacimab in patients who were negative for inhibitor and had prior on-demand treatment. The effect size was clinically significant, and the level of statistical significance was high. The secondary outcome measures had similar effect sizes to the primary outcome measure.

The study also demonstrated superiority for the primary outcome measure of efficacy for marstacimab in patients who were negative for inhibitor and had prior prophylactic treatment. Superiority was also demonstrated for most of the secondary efficacy outcome measures, and non-inferiority for the remainder. However, this is the patient group that is the most likely target population, and for this patient group the effect size was not large and the statistical significance was marginal.

## Study B7841003

Study B7841003 was an open-label, long-term safety and efficacy trial of marstacimab in participants with haemophilia A or haemophilia B, with or without inhibitors. The study was up to one year in duration. The study was a follow-on study from Study B7841002. Participants enrolled in Cohort 1 (300 mg once weekly, without inhibitor group) continued at the 300 mg once weekly dose level, but all other participants were treated with 150 mg once weekly, and

used the same treatment regimens and allocations, except the 450 mg dose level was reduced to 150 mg.

The participants continuing from Study B7841002 within 30 days of the Study B7841003 Day 1 visit did not require screening procedures to confirm eligibility: male participants with severe haemophilia A or haemophilia B of at least 18 years of age and less than 75 years old, with body mass index (BMI) of at least 17.5 and no more than 30.5 kg/m$^2$ and a total body weight of at least 50 kg and no more than 100 kg were eligible to participate in the study. For de novo participants: adolescent males of at least 12 years of age to less than 18 years old with BMI of at least 14 kg/m$^2$ and a total body weight of at least 30 kg (only for Cohort 5) and adults, who had at least 6 acute bleeding episodes (spontaneous/traumatic) during the 6-month period prior to screening were eligible.

The treatment groups were:

- Cohort 1: 300 mg SC, continuing as 300 mg SC
- Cohort 2: 150 mg SC, continuing as 150 mg SC
- Cohort 3: 450 mg SC, continuing as 150 mg SC
- Cohort 4: 300 mg SC (inhibitor subjects), continuing as 300 mg SC
- Cohort 5: adolescents with or without inhibitors, continuing as 150 mg SC
- Cohort 6: adults with inhibitors, continuing as 150 mg SC

Treatments were administered once weekly.

The efficacy outcome measures were:

- frequency and annualised rate of bleeding episodes from Day 1 to Day 393
- frequency of rescue (factor VIII or factor IX) therapy for treatment of breakthrough bleeding episodes.

The safety outcome measures were: treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, and infusion and injection site reactions.

There were 24 subjects screened and 20 were assigned to study treatment and received treatment: 10 in the 300 mg dose group and 10 in the 150 mg dose group. Eighteen subjects completed the study, 9 in each treatment group. Two subjects discontinued due to withdrawal by subject. All the 20 treated subjects were included in the analysis.

All the subjects were male and the age range was 19 to 57 years. There were 14 (70%) white subjects and 6 (30%) Black or African American. The weight range was 50.7 kg to 86.7 kg and the BMI range was 17.9 to 23.4 kg/m$^2$. There were 19 (95%) subjects with haemophilia A and one (5%) with haemophilia B. Thirteen (65%) subjects had haemophilic arthropathy.

The mean (SD) ABR decreased from 20.200 (5.6921) /year to 1.486 (2.4312) /year in the 300 mg treatment group; and from 17.400 (8.9464) /year to 2.699 (4.4561) /year in the 150 mg treatment group. There was only one subject with haemophilia B, so comparisons by dose and haemophilia type were not possible. The one subject with haemophilia B was in the 150 mg cohort and had no bleeding events during the study.

Tissue factor pathway inhibitor concentrations increased to a greater extent in the 300 mg dose group compared to the 150 mg. There was no significant difference between the groups in thrombin generation lag time. The increase in peak thrombin generation was greater in the 300 mg group overall compared to the 150 mg group overall. There was no significant difference between the groups in thrombin generation potential. There was no apparent difference

between the groups in thrombin generation assay endogenous thrombin potential. Prothrombin fragments 1+2 were increased in all the treatment groups throughout the treatment period.

### *Study B7841007*

Study B7841007 was an open-label extension of Study B7841005. The study is planned to continue until marstacimab is commercially available to the participants or for up to 7 years. Hence the study is ongoing and an interim report was provided. The study was conducted at 36 centres in 14 countries: Canada (2 centres), Croatia (2), France (1), Hong Kong (2), India (2), Japan (2), Korea (3), Mexico (1), Oman (2), Serbia (3), Spain (4), Taiwan (1) Turkey (9), and the US (2).

The study used the same efficacy and safety endpoints as for Study B7841005 and the participants continued with their final regimen from that study. The preferred administration method was the PFP but if subjects had difficulty using the PFP they could use the PFS.

The study enrolled adult or adolescent male participants with severe haemophilia A or moderately severe to severe haemophilia B (defined as factor VIII activity less than 1% or factor IX activity ≤ 2%, respectively) with or without inhibitors who successfully completed the Study B7841005.

There were 88 subjects who entered the study: 29 in the on-demand cohort and 59 in the prophylaxis cohort. None of the subjects had inhibitors. Two subjects withdrew (withdrawn by subject). One subject is not included in the analysis because data were not available by the cut-off date.

All the subjects were male. The age range was 13 to 66 years. Fourteen (16.1%) subjects were aged under 18 years and one was aged at least 65 years. The weight range was 39.0 to 128.8 kg. There were 67 (77.0%) subjects with haemophilia A and 20 (23.0%) with haemophilia B. All the subjects were negative for inhibitor.

The median (range) duration of treatment was 193 (34 to 483) days. There were 13 subjects treated for at least 12 months. The median (range) number of exposure days (treatments) was 28 (5 to 68) days (treatments). There were no dose reductions due to adverse events (AEs) during the study. Four participants had their weekly dose increased from 150 mg to 300 mg, as allowed per protocol, due to insufficient clinical response.

The model base mean estimate (95% CI) for ABR was 2.79 (1.90 to 4.09) overall, 3.86 (2.02 to 7.37) for the on-demand group and 2.27 (1.40 to 3.67) for the prophylaxis group. Over the treatment period 13 (44.8%) subjects in the on demand group and 36 (62.1%) in the prophylaxis group had no bleeds.

The model base mean estimate (95% CI) for incidence of joint bleeds was 1.88 (1.29 to 2.74) overall, 1.87 (1.07 to 3.26) for the on-demand group and 1.87 (1.14 to 3.08) for the prophylaxis group.

The model base mean estimate (95% CI) for incidence of spontaneous bleeds was 1.91 (1.26 to 2.89) overall, 2.54 (1.22 to 5.29) for the on-demand group and 1.62 (0.96 to 2.73) for the prophylaxis group.

The model base mean estimate (95% CI) for incidence of targeted joint bleeds was 0.94 (0.54 to 1.63) overall, 0.90 (0.51 to 1.58) for the on-demand group and 0.91 (0.36 to 2.27) for the prophylaxis group.

The model base mean estimate (95% CI) for incidence of total bleeds was 3.59 (2.56 to 5.04) overall, 5.10 (3.25 to 8.00) for the on-demand group and 2.73 (1.70 to 4.38) for the prophylaxis group.

For the prior on-demand group (n = 19) and the prior prophylaxis group (n = 24), the mean change from B7841007 baseline in the total HJHS score at 180 days was 1.1 and -2.7, respectively.

The mean total annualised factor replacement consumption was 9,954.9 IU, and for the prior on-demand group and prior prophylaxis group was 14,807.1 IU and 7,528.8 IU, respectively.

For the Haem-A-QoL, across all participants who reported values at 180 days (n = 42), the mean change from B7841007 baseline at 180 days in the physical health domain and total scores was −0.7 and −0.2, respectively.

There was no change from B7841007 baseline in the EQ-5D-5L index, and the mean change in the EQ-VAS score was −1.8.

A sub-study of the feasibility of the PFP device enrolled 23 subjects. The study found a rapid learning effect for the use of the device. The delivery success rate (DSSR) was 100% at all visits except for Week 2, which had a DSSR of 95.0%, with an overall DSSR across all visits of 99.2%.

## *Commentary on other efficacy studies*

The other efficacy studies were both follow-on studies. The studies demonstrated long-term maintenance of efficacy. There was no apparent loss of effect over the time course of the studies.

## *Assessment of efficacy benefits*

The benefits with strengths and uncertainties for the proposed indication are summarised below.

**Table 4: Assessment of benefits**

| Benefits | Strengths and Uncertainties |
|---|---|
| In the pivotal study, for the non-inhibitor, on-demand group, the mean (95% CI) model based estimate for ABR during the observation period was 38.00 (31.03 to 46.54) /year and during the active treatment phase was 3.18 (2.09 to 4.85) /year, ratio estimate (95% CI) 0.084 (0.059 to 0.119) p < 0.001.<br><br>In this group, efficacy was demonstrated separately for haemophilia A, ratio estimate (95% CI) 0.0894 (0.062 to 0.130) and haemophilia B, ratio estimate (95% CI) 0.036 (0.012 to 0.111).<br><br>Non-inferiority was demonstrated in the non-inhibitor, prophylaxis group, the mean (95% CI) model based estimate for ABR during the observation period was 7.85 (5.09 to 10.61) /year and during the active treatment phase was 5.08 (3.40 to 6.77) /year; rate difference (95% CI) −2.77 (−5.37 to −0.16); non-inferiority criterion was the upper bound of 95% CI less than 2.5.<br><br>Bioequivalence has been demonstrated for the PFS and PFP devices. | The efficacy data are based on a single pivotal study. The study report was described as interim, but the sponsor indicates the analyses presented in the dossier are final. The baseline ABR in the prior prophylaxis population was unusually high and this might bias the estimate of treatment effect because of the phenomenon of deviation towards the mean.<br><br>The target population is primarily the prior prophylaxis group and for this population the effect size was not large and the statistical significance was marginal. |

## Safety

The same studies mentioned above for efficacy looked at safety outcome measures being:

- Study B7841005: the safety outcome measures were AEs, ECGs, vital signs, clinical laboratory tests, ADA and neutralising antibody (NAb)
- Study B7841003 and Study B7841007: the safety outcome measures were AEs, ECGs, vital signs, clinical laboratory tests, ADA and NAb.

There were also 4 clinical pharmacology studies: Study B7841009, Study B7841001, Study B7841010, and Study B7841002.

The safety outcome measures were AEs, ECGs, vital signs, clinical laboratory tests (including clotting studies), ADA and NAb.

Overall, there were 144 subjects with haemophilia, 52 healthy volunteers and 6 Chinese males with haemophilia included in the safety dataset. The median (range) duration of exposure for haemophilia patients was 464 (28 to 847) days. There were 73 subjects treated for at least 12 months up to 18 months, 38 subjects treated for at least 18 months up to 24 months, and 14 subjects treated for at least 24 months.

In Study B7841005 in the non-inhibitor on-demand cohort, there were 22 TEAEs reported in 18 (48.6%) subjects during the observational phase and 35 in 20 (60.6%) subjects during the active treatment phase. In the non-inhibitor prophylaxis cohort, there were 44 TEAEs reported in 25 (27.5%) subjects during the observational phase and 262 in 66 (79.5%) subjects during the active treatment phase. Overall, the most frequently reported TEAEs during the active treatment phase was COVID-19 in 20 (17.2%) subjects, and the timing of COVID-19 might explain the difference between the study phases in TEAEs.

In Study B7841003 there were 15 TEAEs reported in 7 (70%) subjects in the 300 mg group and 24 in 7 (70%) subjects in the 150 mg group. There was no apparent pattern to the TEAEs. Injection site reactions were reported in 2 (20%) subjects in the 300 mg group and one (10%) in the 150 mg group. Erythema was reported in one subject, induration in two and ecchymosis in one.

In Study B7841007 there were 45 TEAEs reported in 27 (31.0%) subjects, including 5 TEAEs reported in 5 (17.2%) subjects in the on-demand group and 40 in 22 (37.9%) subjects in the prophylaxis group. There were 14 TEAEs reported in 4 (28.6%) subjects aged at least 12 years and less than 18 years. The TEAEs were predominantly intercurrent infections and injuries.

In Study B7841009 there were 60 TEAEs reported in 17 (89.5%) of the 19 participants who received marstacimab by PFP. There were 52 TEAEs reported in 15 (83.3%) of the 18 participants who received marstacimab by PFS. The most commonly reported TEAEs were injection site erythema (6 subjects in the PFP group and 3 in the PFS), induration (5 subjects in the PFP group and 3 in the PFS), pain (4 subjects in the PFP group and 5 in the PFS) and haemorrhage (4 subjects in the PFP group and 4 in the PFS).

In Study B7841001 there were 35 TEAEs reported in 20 (62.5%) subjects treated with marstacimab and 20 in 4 (44.4%) subjects treated with placebo. There was one moderate severity TEAE of swollen right foot reported in one subject in the 440 mg IV group (doppler scan negative and not considered to be treatment related).

In Study B7841010 one TEAE was recorded in one subject (upper respiratory tract infection).

In Study B7841002 there were 56 TEAEs in 21 (80.8%) subjects: 16 TEAEs in 7 (100%) subjects in the 300 mg once weekly group, 12 in 4 (66.7%) subjects in the 300/150 mg once weekly group, 15 in 6 (100%) subjects in the 450 mg once weekly group and 13 in 4 (57.1%) subjects in

the 300 mg once weekly inhibitor group. The most frequently reported TEAEs were injection site pain (3 [11.5%] subjects), injection site swelling (3 [11.5%]), and hypertension (3 [11.5%]).

In Study B7841005 there were no deaths. In the non-inhibitor on-demand cohort, serious adverse effects (SAE) were reported in one (2.7%) subject during the observational phase and none during the active treatment phase. In the non-inhibitor prophylaxis cohort, SAEs were reported in 2 (2.2%) subjects during the observational phase and 7 (8.4%) subjects during the active treatment phase. There were no apparent patterns to the SAEs.

In Study B7841003 there were no deaths. Two SAEs were reported in one (10%) subject in the 300 mg group (cerebral haemorrhage, generalised tonic-clonic seizure) and none in the 150 mg group. The cerebral haemorrhage occurred in the context of 'the participant was hit as an innocent bystander with an object against the left temple'.

In Study B7841007 there were no deaths. There were 2 SAEs (contusion of the head, haemarthrosis).

### *Studies with evaluable safety data: dose finding and pharmacology*

In Study B7841009 there were no deaths. There was one SAE in the PFP group: pulmonary embolus.

In Study B7841001 and Study B7841010 there were no deaths or SAEs.

In Study B7841002 there were no deaths. Serious adverse effects were reported in 4 (15.4%) subjects: one (14.3%) subject in the 300 mg once weekly group (appendicitis), one (16.7%) in the 300/150 mg once weekly group (physical assault), one (16.7%) in the 450 mg once weekly group (cholelithiasis) and one (14.3%) in the 300 mg once weekly inhibitor group (haemorrhage).

## *Evaluation's overall conclusions on clinical safety*

There are limited safety data, partly because the studies are incomplete and partly because of the low numbers of subjects in the development program. The sponsor did not provide total numbers of subjects exposed to marstacimab, but from the submitted data it appears that overall, there were 144 subjects with haemophilia, 52 healthy volunteers and 6 Chinese males with haemophilia included in the safety dataset. The duration of exposure is also difficult to assess, but in the Summary of Clinical Safety, there were 73 subjects treated for ≥ 12 to < 18 months, 38 subjects treated for ≥ 18 to <24 months, and 14 treated for ≥ 24 months.

However, the submitted data indicate a favourable safety profile in subjects with haemophilia. The rates of TEAEs in the pivotal study were increased in the active treatment phase compared with the observational phase, but this can be attributed to COVID-19 appearing during the course of the study. In the non-inhibitor on-demand cohort, there were 22 TEAEs reported in 18 (48.6%) subjects during the observational phase and 35 in 20 (60.6%) during the active treatment phase. In the non-inhibitor prophylaxis cohort, there were 44 TEAEs reported in 25 (27.5%) subjects during the observational phase and 262 in 66 (79.5%) during the active treatment phase.

There were few administration site reactions, and these were predominantly of minor severity.

There were no deaths reported during the development program.

There were few SAEs, and one (in a healthy volunteer) that was attributable to treatment.

There were few discontinuations and the changes in treatment dose were predominantly increases in dose in response to breakthrough bleeds.

There were no concerning trends in clinical laboratory tests, including liver function, renal function and haematology.

Few subjects developed persisting ADAs. In the PK analysis ADAs were associated with an increase in clearance of 20%, which was not considered clinically significant. In the pivotal study, there were 6 (5.2%) subjects with NAb, all of which were transient and had resolved by the end of the study. There were no episodes of anaphylaxis or hypersensitivity.

However, in the healthy volunteer population there was one thromboembolic SAE. In Study B7841009 there was one participant with pulmonary embolism. This occurred in a 54-year-old male on study Day 10. He had no prior risk factors for VTE. However, he had received the AstraZeneca COVID vaccine on Days −77 and −20. This event is consistent with the expected timing of marstacimab effects, specifically with the timing of peak thrombin generation, coagulation activation and clot breakdown, as described in the PD data. The PD data indicate greater effect on thrombin generation in the healthy population compared with the haemophilia population. Peak thrombin in healthy subjects was double the value for subjects with haemophilia. This indicates the risk of thromboembolism may be greater in healthy subjects than in subjects with haemophilia.

## *Assessment of risk*

The overall assessment of risks with strengths and uncertainties are summarised below.

Real-world evidence (RWE) and real-world data (RWD) were not included in the submission.

**Table 5: Overall assessment of risk**

| Risks | Strengths and Uncertainties |
|---|---|
| The rates of TEAEs in the pivotal study were increased in the active treatment phase compared with the observational phase, but this can be attributed to COVID-19 appearing during the course of the study. In the non-inhibitor on-demand cohort, there were 22 TEAEs reported in 18 (48.6%) subjects during the observational phase and 35 in 20 (60.6%) subjects during the active treatment phase. In the non-inhibitor prophylaxis cohort, there were 44 TEAEs reported in 25 (27.5%) subjects during the observational phase and 262 in 66 (79.5%) subjects during the active treatment phase.<br><br>There were few administration site reactions, and these were predominantly of minor severity.<br><br>There were no deaths reported during the development program.<br><br>There were few SAEs, and one (in a healthy volunteer) that was attributable to treatment. This event was deep venous thrombosis and pulmonary embolism and resulted in the premature termination of the trial.<br><br>There were few discontinuations and the changes in treatment dose were predominantly increases in dose in response to breakthrough bleeds.<br><br>There were no concerning trends in clinical laboratory tests, including liver function, renal function and haematology.<br><br>Few subjects developed persisting ADAs. In the PK analysis ADAs were associated with an increase in clearance of 20%, which was not considered clinically significant. In the pivotal study, there were 6 (5.2%) subjects with NAb, all of which were transient and had resolved by the end of the study. There were no episodes of anaphylaxis or hypersensitivity. | There are limited safety data, partly because the studies are incomplete and partly because of the low numbers of subjects in the development program.<br><br>Two similar products have had interruptions in development because of thromboembolic events: concizumab (Alhemo) and befovacimab.<br><br>The risk of thromboembolism may be greater in healthy volunteers because of a greater effect on thrombin generation. This may also indicate a greater risk in patients with mild or moderate severity haemophilia.<br><br>The sponsor has reported a single case of venous thrombosis occurring in a patient treated with marstacimab.<br><br>The sponsor assesses that the risks of thromboembolism in patients treated with marstacimab are similar to similar patients treated with emicizumab (Hemlibra). These risks could be addressed with strengthened warnings and patient education. |

# Risk management plan

The summary of safety concerns and their associated risk monitoring and mitigation strategies is provided below. The TGA may request an updated risk management plan (RMP) at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

**Table 6: Summary of safety concerns**

| Summary of safety concerns | | Pharmacovigilance | | Risk minimisation | |
|---|---|---|---|---|---|
| | | Routine | Additional | Routine | Additional |
| **Important identified risks** | Nil | – | – | – | – |
| **Important potential risks** | Thromboembolism | ✓ | ✓* | ✓ | – |
| **Missing information** | Use in pregnancy† | ✓ | – | ✓ | – |
| | Use in lactation† | ✓ | – | ✓ | – |
| | Use in female patients† | ✓ | – | – | – |
| | Patients with current or history of cardiovascular conditions (coronary artery disease / thrombosis/ ischaemic disease)† | ✓ | – | ✓ | – |
| | Use in elderly patients† | ✓ | – | ✓ | – |
| | Use in moderate to severe hepatic impairment† | ✓ | – | ✓ | – |
| | Long-term use† | ✓ | – | – | – |

* Post Authorisation Safety Study (PASS) (B7841016)

† Australian specific safety concern

The summary of safety concerns proposed in the Australia-specific annex (ASA) aligns with the draft EU-RMP with additional Australian specific missing information categories. The summary of safety concerns is acceptable from an RMP perspective.

The proposed pharmacovigilance (PV) plan in the ASA aligns with the PV plan in the draft EU-RMP which includes routine PV as well as additional PV to address 'thromboembolism' in the form of a Post Authorisation Safety Study (PASS). The Australian specific missing information categories will be further characterised by routine PV activities. The PV plan is acceptable from an RMP perspective.

Routine risk minimisation activities have been proposed in the ASA for all safety concerns except missing information 'use in female patents' and 'long term use'. No additional risk minimisation has been proposed. This is acceptable from an RMP perspective.

The RMP evaluation recommended conditions of registration relating to the versions of the risk management plan, requirement for periodic safety update reports, and inclusion of the medicine in the Black Triangle Scheme.

# Risk-benefit analysis

## *Delegate's considerations*

Marstacimab is proposed for the routine prophylaxis of patients aged 12 years and older for severe haemophilia A and haemophilia B with no factor VIII or factor IX inhibitors respectively. The key data are based on a single pivotal study which was open-label and a single-arm, sequential crossover design.

## *Efficacy*

In the pivotal study, for the non-inhibitor, on-demand group, the mean (95% CI) model-based estimate for ABR during the observation period was 38.00 (31.03 to 46.54) /year and during the active treatment phase was 3.18 (2.09 to 4.85) /year, ratio estimate (95% CI) 0.084 (0.059 to 0.119) $p < 0.001$.

In this group, efficacy was demonstrated separately for haemophilia A, ratio estimate (95% CI) 0.0894 (0.062 to 0.130) and haemophilia B, ratio estimate (95% CI) 0.036 (0.012 to 0.111).

Non-inferiority was demonstrated in the non-inhibitor, prophylaxis group, the mean (95% CI) model based estimate for ABR during the observation period was 7.85 (5.09 to 10.61) /year and during the active treatment phase was 5.08 (3.40 to 6.77) /year, rate difference (95% CI) −2.77 (−5.37 to −0.16), non-inferiority criterion was the upper bound of 95% CI less than 2.5.

## *Strengths and uncertainties of efficacy*

The efficacy data are based on a single pivotal study. The study report was described as interim, but the sponsor indicates the analyses presented in the dossier are final. The baseline ABR in the prior prophylaxis population was unusually high and this might bias the estimate of treatment effect because of the phenomenon of deviation towards the mean.

The target population is primarily the prior prophylaxis group and for this population the effect size was not large and the statistical significance was marginal.

## *Safety*

The rates of TEAEs in the pivotal study were increased in the active treatment phase compared with the observational phase, but this can be attributed to COVID-19 appearing during the course of the study. In the non-inhibitor on-demand cohort, there were 22 TEAEs reported in 18 (48.6%) subjects during the observational phase and 35 in 20 (60.6%) subjects during the active treatment phase. In the non-inhibitor prophylaxis cohort, there were 44 TEAEs reported in 25 (27.5%) subjects during the observational phase and 262 in 66 (79.5%) subjects during the active treatment phase.

There were few administration site reactions, and these were predominantly of minor severity.

There were no deaths reported during the development program.

There were few SAEs, and one (in a healthy volunteer) that was attributable to treatment. This event was deep venous thrombosis and pulmonary embolism and resulted in the premature termination of the trial.

There were few discontinuations and the changes in treatment dose were predominantly increases in dose in response to breakthrough bleeds.

There were no concerning trends in clinical laboratory tests, including liver function, renal function and haematology.

Few subjects developed persisting ADAs. In the PK analysis ADAs were associated with an increase in clearance of 20%, which was not considered clinically significant. In the pivotal study, there were six (5.2%) subjects with NAb, all of which were transient and had resolved by the end of the study. There were no episodes of anaphylaxis or hypersensitivity.

### *Strengths and uncertainties of risk*

There are limited safety data, partly because the studies are incomplete and partly because of the low numbers of subjects in the development program.

Two similar products have had interruptions in development because of thromboembolic events: concizumab (Alhemo) and befovacimab.

The risk of thromboembolism may be greater in healthy volunteers because of a greater effect on thrombin generation. This may also indicate a greater risk in patients with mild or moderate severity haemophilia.

The sponsor has reported a single case of venous thrombosis occurring in a patient treated with marstacimab.

The sponsor assesses that the risks of thromboembolism in patients treated with marstacimab are similar to similar patients treated with emicizumab (Hemlibra). These risks could be addressed with strengthened warnings and patient education.

### *Proposed action*

Marstacimab is approvable for the routine prophylaxis of bleeding episodes in patients 12 years of age and older 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.

# Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Hympavzi (marstacimab) 150 mg/mL solution for injection in prefilled pen, indicated for:

> *Hympavzi is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older 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.*

## Specific conditions of registration

- Hympavzi (marstacimab) is to be included in the Black Triangle Scheme. The PI and CMI for Hympavzi must include the black triangle symbol and mandatory accompanying text for 5 years, which starts from the date of first supply of the product.
- The Hympavzi EU-Risk Management Plan (RMP) (version 0.3, dated 6 August 2024, data lock point 17 April 2023), with Australian Specific Annex (version 1.1, dated 19 August 2024), included with submission PM-2024-00030-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than 3 years from the date of the approval letter. The annual submission may be made up of 2 PSURs each covering 6 months. If the sponsor wishes, the 6-monthly reports may be submitted separately as they become available.

  If the product is approved in the EU during the 3 years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than 3 years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must be submitted within 90 calendar days of the data lock point for that report.
- Laboratory testing and compliance with Certified Product Details
  - All batches of Hympavzi supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results Laboratory test results | Therapeutic Goods Administration (TGA) and periodically in testing reports on the TGA website.
- Certified Product Details
  - The CPD, as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.
  - A template for preparation of CPD for biological prescription medicines can be obtained from the TGA website

- [for the form] https://www.tga.gov.au/form/certified-product-details-cpd-biologicalprescription medicines
- [for the CPD guidance] https://www.tga.gov.au/guidance-7-certified-product-details.

# Product Information (PI) and Consumer Medicine Information (CMI)

For the most recent Product Information (PI) and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

**Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au  Phone: 1800 020 653  Fax: 02 6203 1605
**https://www.tga.gov.au**

Reference/Publication #