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▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/safety/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – HYMPAVZI™ (MARSTACIMAB)

1. NAME OF THE MEDICINE

Marstacimab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prefilled pen contains 150 mg marstacimab in 1 mL of solution.

Marstacimab is a human monoclonal immunoglobulin G Type 1 (IgG1) antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipients with known effect

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear and colourless to light yellow with pH of 5.8.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Dose and method of administration

Treatment should be initiated under the supervision of a physician/healthcare professional experienced in the treatment of haemophilia.

Posology

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.

Duration of treatment

Hympavzi is intended for long-term prophylactic treatment.

Dose adjustments during treatment

A dose adjustment to 300 mg subcutaneous injection weekly can be considered in patients weighing ≥50 kg when control of bleeding events is judged to be inadequate by the healthcare professional. There are insufficient data to recommend doses above 300 mg weekly.

Missed dose

If a dose is missed, administer as soon as possible before the day of the next scheduled dose, and then resume usual weekly dosing schedule.

If the missed dose is more than 13 days after the last dose, then a loading dose of 300 mg by subcutaneous injection should be administered followed thereafter by a resumption of 150 mg by subcutaneous injection once weekly.

Switching to Hympavzi

Switching from prophylactic factor replacement therapy to Hympavzi: Prior to initiation of Hympavzi, patients should discontinue treatment with clotting factor concentrates (factor VIII/factor IX concentrates). Patients can initiate Hympavzi at any time after discontinuing clotting factor concentrates.

Switching from non-factor-based haemophilia medicinal products to Hympavzi: No clinical trial data are available to guide converting patients from non-factor-based medicinal products to Hympavzi. Although a washout period has not been studied, one approach is to allow an adequate washout period (at least 5 half-lives) of the prior agent based on labelled half-life before initiating treatment with Hympavzi. Haemostatic support with clotting factor concentrates may be needed during the switch from other non-factor-based haemophilia medicinal products to Hympavzi.

Method of administration

Hympavzi is for subcutaneous injection only.

Hympavzi is intended for use under the guidance of a healthcare professional. After proper training in subcutaneous injection technique, a patient or caregiver may inject Hympavzi if a physician/healthcare professional determines that it is appropriate.

Prior to subcutaneous administration, Hympavzi may be removed from the refrigerator and allowed to warm at room temperature in the carton for 15 to 30 minutes and protected from direct sunlight. Hympavzi should not be warmed by using a heat source such as hot water or a microwave. After removal of Hympavzi from the refrigerator, Hympavzi must be used within 7 days or discarded (see section 6.4 Special precautions for storage).

Hympavzi should be administered by subcutaneous injection, once weekly, at any time of day. The recommended injection sites are the abdomen and thigh. Other locations are acceptable if required. Administration of Hympavzi in the buttocks should be performed by a caregiver or healthcare professional only.

For the 300 mg loading dose, each of the two Hympavzi 150 mg injections should be administered at different injection sites.

It is recommended to rotate the injection site with each injection. Hympavzi should not be administered into bony areas or areas where the skin is bruised, red, tender or hard, or areas where there are scars or stretch marks. Hympavzi should not be injected into a vein.

During treatment with Hympavzi, other medicinal products for subcutaneous administration should, preferably, be injected at different anatomical sites.

Refer to the Instructions for Use for complete administration instructions.

Special populations

Guidance on use with breakthrough bleed treatments

Factor VIII and factor IX products can be administered for the treatment of breakthrough bleeds in patients receiving Hympavzi. Additional doses of Hympavzi should not be used to treat breakthrough bleeding events. Healthcare professionals should discuss with all patients and/or caregivers about the dose and schedule of clotting factor concentrates to use, if required, while receiving Hympavzi prophylaxis, including using the lowest possible effective dose of clotting factor concentrate (see section 4.4 Special warnings and precautions for use). Please refer to the product information for the clotting factor concentrate being used.

Hepatic impairment

No dose adjustments are recommended in patients with mild hepatic impairment (see section 5.2 Pharmacokinetic properties). Marstacimab has not been studied in patients with moderate or severe hepatic impairment.

Renal impairment

No dose adjustments are recommended in patients with mild renal impairment (see section 5.2 Pharmacokinetic properties). Marstacimab has not been studied in patients with moderate or severe renal impairment.

Elderly population

No dose adjustments are recommended in patients over 65 years of age. There are limited data in patients over 65 years of age.

Paediatric population

The safety and efficacy of Hympavzi in paediatric patients <12 years of age have not yet been established. The safety and efficacy of marstacimab in adolescents with a body weight <35 kg have not been established. No data are available.

Management in the perioperative setting

The safety and efficacy of Hympavzi have not been formally evaluated in the surgical setting. Patients have had minor surgical procedures without discontinuing Hympavzi prophylaxis in clinical studies.

For major surgery, Hympavzi should be discontinued, and management initiated per local standard of care with clotting factor concentrate and measures to manage the risk of venous thrombosis which can be elevated in the perioperative period. Consult the product information for the clotting factor concentrate for dosage guidelines in patients with haemophilia undergoing major surgery. Resumption of Hympavzi therapy should take into account the overall clinical status of the patient, including the presence of post-surgical thromboembolic risk factors, use of other haemostatic products and other concomitant medications (see Missed dose section above).

Management in patients with acute severe illness

There is limited experience with the use of Hympavzi in patients with acute severe illness. Reasons to consider temporary dose interruption of Hympavzi include occurrence of acute severe illness (e.g., serious infection, sepsis, trauma) in which there may be increased activation of coagulation and which the physician/healthcare professional considers could increase the risks associated with Hympavzi administration. Treatment of acute severe illness should be managed per local standard of care and continued treatment with Hympavzi in this situation should be weighed against the potential risks involved. Hympavzi therapy can be resumed once patient has clinically recovered (see Missed dose section above).

4.3 Contraindications

Hypersensitivity to marstacimab or to any of the excipients listed in Section 6.1 List of excipients.

4.4 Special warnings and precautions for use

Thromboembolic events

Removal of TFPI inhibition may increase a patient's coagulation potential and contribute to a patient's individual, multifactorial risk for thromboembolic events. Thrombotic events with one resulting in a thromboembolism have been observed in clinical studies with Hympavzi (see Section 4.8 Adverse effects (undesirable effects)). The following patients may be at an increased risk of thromboembolic events with use of this medicinal product:

- patients with a history of coronary artery disease, venous or arterial thrombosis or ischaemic disease.
- patients with known risk factors for thromboembolism, including but not limited to genetic prothrombotic conditions (e.g. Factor V Leiden gene mutation), patients with prolonged periods of immobilization, obesity, and smoking.
- patients currently experiencing an acute severe illness with increased tissue factor expression (such as serious infection, sepsis, trauma, crush injuries, cancer).

Hympavzi has not been studied in patients with a history of previous thromboembolic events and there is limited experience in patients with acute severe illness.

The use of anti-tissue factor pathway inhibitor (anti-TFPI) products has been associated with the development of thromboembolic complications. Hympavzi has not been studied in patients with a history of previous thromboembolic events (see section 5.1 Pharmacodynamic properties). Interrupt Hympavzi prophylaxis if diagnostic findings consistent with thromboembolism occur and manage as clinically indicated.

Factor VIII and factor IX products have been safely administered for the treatment of breakthrough bleeds in patients receiving Hympavzi. If factor VIII or factor IX products are indicated in a patient receiving Hympavzi prophylaxis, the minimum effective dose of factor VIII/factor IX product according to the product label is recommended.

Consider the benefit and risk of using Hympavzi in patients with a history of thromboembolic events.

Hypersensitivity reactions

Cutaneous reactions of rash and pruritus that may reflect drug hypersensitivity have occurred in Hympavzi-treated patients (see section 4.8 Adverse effects). If Hympavzi-treated patients develop a severe hypersensitivity reaction, advise patients to discontinue Hympavzi and seek immediate emergency treatment.

Use in hepatic impairment

Hympavzi is not recommended in patients with moderate or severe hepatic impairment. See section 4.2 Dose and method of administration.

Use in renal impairment

Hympavzi is not recommended in patients with moderate or severe renal impairment. See section 4.2 Dose and method of administration.

Use in the elderly

There is limited data with marstacimab in patients aged 65 years or older.

Paediatric use

The safety and efficacy of Hympavzi in paediatric patients less than 12 years of age have not yet been established. The safety and efficacy of marstacimab in adolescents with a body weight <35 kg have not been established. No data are available.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

No clinical drug interaction studies with marstacimab have been conducted.

As a monoclonal antibody (mAb), marstacimab is expected to be cleared by catabolism following endocytosis by the mononuclear phagocytic system. Since the elimination of mAbs does not occur through non-catabolic pathways such as hepatic metabolic enzymes (i.e., cytochrome P450 enzymes) or via small molecule renal/hepatic drug transporters,

pharmacokinetic (PK) interactions with concomitant medications that are eliminated via these pathways are unlikely. Indirect effect of a biologic such as marstacimab on the expression of cytochrome P450 enzymes is also not expected.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No fertility data are available in humans. Marstacimab did not affect fertility when administered intravenously to male rats at doses up to 1000 mg/kg/week (yielding exposure more than 150 times higher than in patients at the maximum recommended clinical dose of 300 mg/week subcutaneously based on plasma AUC). No fertility study has been performed in female animals. No microscopic changes in male or female reproductive organs to indicate likely impairment of fertility in patients were observed in the repeat-dose toxicity studies conducted with marstacimab in rats and cynomolgus monkeys. The highest doses tested in these studies (1000 mg/kg/week in rats and 500 mg/kg/week in monkeys, administered intravenously) yielded exposure approximately 150-165 times higher than in patients at a clinical dose of 300 mg/week subcutaneously based on plasma AUC.

Use in pregnancy – Pregnancy Category D

Women of childbearing potential receiving Hympavzi should use effective contraception during, and for at least 1 month after cessation of Hympavzi treatment.

There are no data available for marstacimab in pregnant women and no embryofetal development studies have been performed in animals. TFPI, the target of marstacimab, is recognised to be critical for development, with its knockout in mice associated with embryofetal lethality. As an IgG antibody, placental transfer of marstacimab is expected, increasing in a linear fashion as pregnancy progresses.

Hympavzi is not recommended for use in pregnant women due to possible embryofetal harm.

Use in lactation

Lactation studies have not been conducted in humans or animals. It is not known whether marstacimab is excreted in human milk. Human IgG is known to be present in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Hympavzi therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

No studies on the effect of ability to drive or use machines have been performed. No effects on the ability to drive and use machines have been observed.

4.8 Adverse effects (undesirable effects)

Summary of the safety profile

The most frequently reported adverse reactions after treatment with Hympavzi were injection site reactions (ISRs) (11.2%).

Tabulated list of adverse reactions

Safety data are based on pooled data from the Phase 3 safety and efficacy study (BASIS) and its ongoing open-label extension (OLE) study. The Phase 3, multi-centre study was conducted in adolescent and adult patients with severe (coagulation factor activity <1%) haemophilia A or B between ages 12 to <75 years without inhibitors comparing factor-based therapy to Hympavzi prophylaxis (see section 5.1 Pharmacodynamic properties). The data from the Phase 3 study 12-month active treatment period reflects exposure of 116 male patients with haemophilia A or B without inhibitors to Hympavzi administered once weekly. Ninety-seven (83.6%) patients were adults (18 years of age and older) and 19 (16.4%) were adolescents (12 years up to <18 years). A total of 87 of the 116 patients completing the 12-month treatment period subsequently enrolled in the OLE study. The median duration of exposure was 518.5 days (range 28 to 847 days).

Table 1 summarises the adverse drug reactions (ADR) listed by MedDRA system organ class reported in patients who received Hympavzi prophylaxis.

Table 1. Adverse drug reactions

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100
Nervous system disorders		Headache	
Vascular disorders		Hypertension	Thrombosis
Skin and subcutaneous tissue disorders		Pruritus	Rash
General disorders and administration site conditions	Injection site reactions[a]		

a. Injection site reactions include: injection site bruising, injection site erythema, injection site haematoma, injection site induration, injection site oedema, injection site pain, injection site pruritus, injection site swelling.

A tabulated summary of treatment-emergent adverse events occurring in ≥1% of patients is provided in Table 2.

Table 2. Number (%) of Patients with Treatment-Emergent Adverse Events Occurring with a Frequency of ≥1%

Preferred Term N=116	Active n/N (%)
GASTROINTESTINAL DISORDERS	
Dental caries	5 (4.3)
Haemorrhoids	3 (2.6)
Diarrhoea	2 (1.7)

Preferred Term **N=116**	**Active** **n/N (%)**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Injection site pruritus	4 (3.4)
Injection site erythema	3 (2.6)
Injection site swelling	3 (2.6)
Fatigue	2 (1.7)
Injection site bruising	2 (1.7)
Injection site induration	2 (1.7)
Injection site pain	2 (1.7)
Peripheral swelling	2 (1.7)
Pyrexia	2 (1.7)
INFECTIONS AND INFESTATIONS	
COVID-19	22 (19.0)
Nasopharyngitis	5 (4.3)
Tonsillitis	4 (3.4)
Pharyngitis	3 (2.6)
Upper respiratory tract infection	3 (2.6)
Herpes zoster	2 (1.7)

Data from clinical trials B7841005/B7841007 – no placebo comparator.

Description of selected adverse reactions

Injection site reactions (ISRs)

In total, 13 (11.2%) patients treated with Hympavzi reported ISRs. The majority of ISRs observed in Hympavzi clinical trials were transient and reported as mild to moderate in severity. No occurrences of injection site reaction led to a dose adjustment or drug discontinuation.

Rash

In the non-inhibitor population, one (0.9%) patient reported non-serious rash (Grade 1).

In the inhibtor population of an ongoing clinical study in which 35 haemophilia patients with inhibitors are treated with Hympavzi, one (2.9%) patient with severe haemophilia B and a history of allergic reaction to exogenous factor IX experienced severe rash with onset at approximately 9 months. The patient required a prolonged course of oral corticosteroids for resolution and treatment with marstacimab was discontinued.

Paediatric population

The paediatric population studied comprises a total of 19 adolescent patients (from 12 to <18 years of age). The safety profile of Hympavzi was overall consistent between adolescents and adults.

Post marketing experience

The limited post-marketing experience with this marstacimab is consistent with the above profile.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/safety/reporting-problems.

4.9 Overdose

Doses of marstacimab >600 mg within a 6-day (144-hour) time period have not been studied.

Patients who receive an accidental overdose should immediately contact their physician/healthcare provider and be monitored closely.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Marstacimab is a human monoclonal IgG1 antibody directed against the Kunitz domain 2 (K2) of tissue factor pathway inhibitor (TFPI), the primary inhibitor of the extrinsic coagulation cascade. Marstacimab's binding to TFPI prevents TFPI's inhibition of factor Xa (FXa). Thus, neutralising the activity of TFPI may serve to enhance the extrinsic pathway and bypass the need for replacement FVIII or FIX.

Pharmacodynamic effects

Consistent with its anti-TFPI mechanism, marstacimab administration to haemophilia patients causes an increase in total TFPI and downstream biomarkers of thrombin generation such as prothrombin fragments 1+2, peak thrombin, and D-Dimer. These changes were reversible after treatment discontinuation. Marstacimab therapy does not produce clinically meaningful changes in standard measures of coagulation including activated Partial Thromboplastin Time (aPTT) and Prothrombin Time (PT).

Clinical trials

Clinical studies in adult and adolescent patients with haemophilia A without FVIII inhibitors or haemophilia B without FIX inhibitors

Patients (aged ≥12 years old and ≥35 kg) with haemophilia A without inhibitors and haemophilia B without inhibitors (Study B7841005/BASIS)

The pivotal Phase 3 study (BASIS) was a one-way, cross-over, open-label, multi-centre study in 116 adult and adolescent males (aged 12 years and older and ≥35 kg) with severe haemophilia A (FVIII <1%) without FVIII inhibitors or severe haemophilia B (FIX <1%) without FIX inhibitors who previously received on-demand (N = 33) or prophylactic (N = 83) treatment with FVIII or FIX. Patients with previous or current treatment for or history of

coronary artery disease, venous or arterial thrombosis or ischaemic disease were excluded from the study.

The study population was characterised by a severe bleeding phenotype. The mean annualised bleeding rates (ABR) for treated bleeds were 38.00 and 7.85 in the Observational Phase for the on-demand and prophylaxis cohorts, respectively, prior to crossing over to weekly marstacimab prophylaxis. All (100%) patients in the on-demand cohort had one or more target joints at study entry and 36% had 3 or more target joints at study entry. In the routine prophylaxis cohort, 56.6% of the patients had one or more target joints at study entry and 15.7% had 3 or more target joints at study entry.

After a 6-month Observational Phase in which patients received either on-demand or routine prophylactic factor-based therapy, patients received an initial 300 mg loading dose of marstacimab followed by maintenance doses of 150 mg of marstacimab once weekly for 12 months. Dose escalation to 300 mg of marstacimab once weekly was allowed after 6 months for patients weighing ≥50 kg experiencing 2 or more breakthrough bleeds. Fourteen (12.1%) out of 116 patients who received marstacimab for at least 6 months underwent dose escalation of their maintenance dose.

The mean age across the treatment groups was 32.4 years (min 13, max 66); 16.4% of patients were 12 to <18 years, and 83.6% were ≥18 years, 100% were male. In this study 48.3% of patients were White, 50.0% were Asian, 0.9% were Black or African American, and 0.9% race information missing; 10.3% of patients identified as Hispanic or Latino. All patients were non-inhibitors (78.4% haemophilia A, 21.6% haemophilia B).

Patients with routine prophylactic factor-based therapy in observational phase

The primary efficacy objective of the study was to compare marstacimab prophylaxis during the Active Treatment Phase versus routine prophylactic factor-based therapy in the Observational Phase as measured by the annualised bleeding rate (ABR) of treated bleeds. Other key efficacy objectives of the study included evaluation of marstacimab prophylaxis in comparison with routine prophylactic factor-based therapy as measured by the incidences of spontaneous bleeds, joint bleeds, target joint bleeds and total bleeds, as well as assessing patients' health-related quality of life (HRQoL).

Table 3 shows the efficacy results of marstacimab prophylaxis compared with routine prophylactic factor-based therapy. Marstacimab demonstrated non-inferiority and superiority over routine prophylactic factor-based therapy as measured by ABR of treated bleeds.

Table 3. Comparison of annualised bleeding rate with marstacimab prophylaxis versus previous routine factor-based prophylaxis in patients ≥12 years of age without factor VIII or factor IX inhibitors

Endpoints in the Order of Testing Hierarchy	**Routine Factor-Based Prophylaxis during 6-Month OP (N = 83)**	**Marstacimab Prophylaxis during 12-Month ATP (N = 83)**
Treated Bleeds (Primary)		
ABR, model-based (95% CI)	7.85 (5.09, 10.61)	5.08 (3.40, 6.77)
Difference vs. RP (95% CI)	-2.77 (-5.37, -0.16) p-value = 0.0376*	
Participants with 0 bleeds, n (%)	33 (39.8)	29 (34.9)
Spontaneous Bleeds, Treated		

ABR, model-based (95% CI)	5.86 (3.54, 8.19)	3.78 (2.25, 5.31)
Difference vs. RP (95% CI)	-2.09 (-4.23, 0.06) Non-inferiority*	
Joint Bleeds, Treated		
ABR, model-based (95% CI)	5.66 (3.33, 7.98)	4.13 (2.59, 5.67)
Difference vs. RP (95% CI)	-1.53 (-3.70, 0.64) Non-inferiority*	
Total Bleeds, Treated & Untreated		
ABR, model-based (95% CI)	8.84 (5.97, 11.72)	5.97 (4.13, 7.81)
Difference vs. RP (95% CI)	-2.87 (-5.61, -0.12) Non-inferiority*	
Target Joint Bleeds, Treated		
ABR, model-based (95% CI)	3.36 (1.59, 5.14)	2.51 (1.25, 3.76)
Difference vs. RP (95% CI)	-0.86 (-2.41, 0.70) Non-inferiority*	

*****Criterion Met (Non-inferiority/p-value if met superiority)

- The protocol specified non-inferiority criterion (upper bound of the 95% CI for the difference) was 2.5 for treated bleeds, spontaneous bleeds, joint bleeds; 1.2 for target joint bleeds; 2.9 for total bleeds. If the non-inferiority criterion was met, superiority was subsequently tested and established if the confidence interval excluded zero.
- p-value is for the superiority testing.
- The estimated mean, difference, and confidence intervals (CIs) for the ABR come from negative binomial regression model.
- Bleed definitions adapted based on ISTH criteria.
- Treated bleeds = bleeds treated with FVIII or FIX
- Total bleeds = bleeds treated and not treated with FVIII or FIX
- ABR = Annualised Bleeding Rate; CI = confidence interval; OP = Observational Phase; ATP = Active Treatment Phase; RP = routine prophylaxis

Patients with on-demand factor-based therapy in observational phase

Among the 33 patients with previous on-demand factor-based therapy treated with Hympavzi, the mean age was 31.9 years (min 15, max 58); 6.1% of patients were 12 to <18 years, and 93.9% were ≥18 years, 100% were male. In this treatment group 33.3% of patients were White and 66.7% were Asian; 9.1% of patients identified as Hispanic or Latino. All patients were non-inhibitors (78.8% hemophilia A, 21.2% hemophilia B).

Table 4 shows the efficacy results of Hympavzi prophylaxis compared with on-demand factor-based therapy. Hympavzi prophylaxis demonstrated superiority over on-demand factor-based therapy in incidences of treated bleeds, spontaneous bleeds, joint bleeds, total bleeds and target joint bleeds.

Table 4. Comparison of annualized bleeding rate with Hympavzi prophylaxis versus on-demand factor-based therapy in patients ≥12 years of age without factor VIII or factor IX inhibitors

Endpoints in the Order of Testing Hierarchy	On-Demand Factor-Based Therapy during 6-Month OP (N = 33)	Hympavzi Prophylaxis during 12-Month ATP (N = 33)
Treated Bleeds (Primary)		
ABR, model-based (95% CI)	38.00 (31.03, 46.54)	3.18 (2.09, 4.85)
Ratio vs. OD (95% CI) p-value	0.084 (0.059, 0.119) <0.0001	
Participants with 0 bleeds, n (%)	1 (3.0)	10 (30.3)
Spontaneous Bleeds, Treated		
ABR, model-based (95% CI)	30.93 (24.12, 39.67)	2.44 (1.61, 3.69)
Ratio vs. OD (95% CI) p-value	0.079 (0.054, 0.114) <0.0001	
Joint Bleeds, Treated		
ABR, model-based (95% CI)	32.86 (26.15, 41.29)	2.83 (1.81, 4.44)
Ratio vs. OD (95% CI) p-value	0.086 (0.059, 0.125) <0.0001	
Total Bleeds, Treated & Untreated		
ABR, model-based (95% CI)	47.76 (39.60, 57.60)	7.39 (5.08, 10.74)
Ratio vs. OD (95% CI) p-value	0.155 (0.116, 0.207) <0.0001	
Target Joint Bleeds, Treated		
ABR, model-based (95% CI)	23.18 (17.20, 31.24)	1.84 (1.06, 3.17)
Ratio vs. OD (95% CI) p-value	0.079 (0.051, 0.124) <0.0001	

- Superiority of Hympavzi is declared when the 95% CI of the ABR ratio lies below 0.5.
- p-value for the null hypothesis that the ratio = 0.5.
- The estimated mean, ratio, and confidence intervals (CIs) for the ABR come from negative binomial regression model.
- Bleed definitions adapted based on ISTH criteria.
- Treated bleeds = bleeds treated with FVIII or FIX
- Total bleeds = bleeds treated and not treated with FVIII or FIX
- ABR = Annualized Bleeding Rate; CI = Confidence Interval; OD = On-Demand; OP = Observational Phase; ATP = Active Treatment Phase

Study B7841007 interim analysis

In the open-label extension (OLE) of the pivotal Phase 3 study, 87 patients received marstacimab at the doses established during participation in the B7841005 study (i.e., 150 mg or 300 mg subcutaneously once weekly) for up to an additional 16 months (mean 7 months)

where marstacimab was shown to maintain long-term (>12 months) efficacy with no new safety signals identified.

Descriptive analyses were conducted to assess marstacimab prophylaxis over time. The model-based mean and other descriptive summaries for the ABR of treated bleeds are shown in Table 5.

Table 5. Annualised bleeding rate with marstacimab prophylaxis over time in patients ≥12 years of age without factor VIII or factor IX inhibitors

Endpoint	Time Interval		
	First 6 Months of ATP (N = 116)	Second 6 Months of ATP (N = 112)	B7841007* (N = 87)
Treated Bleeds			
Mean ABR (95% CI)	4.95 (3.67, 6.68)	3.25 (2.38, 4.42)	2.79 (1.90, 4.09)
Median ABR (IQR)	2.00 (0.00, 5.99)	1.91 (0.00, 4.09)	0.00 (0.00, 4.10)

*Patients received marstacimab for up to an additional 16 months (mean 7 months) during B7841007.

- The estimated mean and confidence intervals (CIs) for the ABR come from negative binomial regression model.
- The median and the interquartile range (IQR), 25th percentile to 75th percentile, for the ABR comes from the descriptive summary.
- ABR = Annualised Bleeding Rate; CI = confidence interval; IQR = interquartile range; ATP = Active Treatment Phase (B7841005); N = number of patients who contributed data for analyses at each time interval

Health-related outcome measures (Study B7841005)

The pivotal Phase 3 study evaluated patient-reported haemophilia-related quality of life outcomes with the Haemophilia-Specific Quality of Life (Haem-A-QoL) questionnaire, for which the Physical Health Domain Score (i.e., painful swellings, presence of joint pain, pain with movement, difficulty walking far and needing more time to get ready) and Total Score (summary of all scores) were protocol defined endpoints of interest. To measure change in health status, the Index Score and the Visual Analog Scale (VAS) from the EuroQoL Five-Dimension Five-Levels Questionnaire (EQ-5D-5L) were examined.

Table 6 and Table 7 provide a comparison of the change from baseline at 6 months between prophylactic marstacimab weekly during the Active Treatment Phase and routine prophylactic factor-based therapy during the Observational Phase on the Physical Health Domain Score and Total Score in Haem-A-QoL, and Index Score and Visual Analog Scale in EQ-5D-5L, respectively. The improvement observed with weekly marstacimab prophylaxis was non-inferior to that observed with routine prophylactic factor-based therapy in these endpoints.

Table 6. Comparison of the change from baseline at 6 months of Haem-A-QoL Physical Health Domain and Total Score with marstacimab prophylaxis during ATP versus previous routine factor-based prophylaxis during OP in patients ≥17 years of age without factor VIII or factor IX inhibitors

Haem-A-QoL Scores	Routine Factor-Based Prophylaxis during 6-month OP (N = 63)	Marstacimab Prophylaxis during 12-month ATP (N = 63)
Physical Health Domain Score		
Median Estimate (95% CI)	-3.0 (-8.2, 2.2)	-6.1 (-12.6, 0.4)
Estimated Difference (95% CI)	-2.2 (-9.1, 4.6) Non-inferiority*	
Total Score		
Median Estimate (95% CI)	-1.2 (-3.5, 1.1)	-3.7 (-6.8, -0.6)
Estimated Difference (95% CI)	-2.8 (-6.6, 1.0) Non-inferiority*	

*****Criterion Met (Non-inferiority/p-value if met superiority)

- Haem-A-QoL scales range from 0 to 100; lower scores are reflective of better haemophilia quality of life.
- For physical health domain score in Haem-A-QoL, the non-inferiority criterion was 10 (Upper Bound of difference CI <10).
- For total score in Haem-A-QoL, the non-inferiority criterion was 7 (Upper Bound of difference CI <7)
- If the non-inferiority criterion was met, superiority was to be tested per testing hierarchy.
- CI = confidence interval, OP = Observational Phase; ATP = Active Treatment Phase

Table 7. Comparison of the change from baseline at 6 months of EQ-5D-5L scores with marstacimab prophylaxis during ATP versus previous routine factor-based prophylaxis during OP in patients ≥12 years of age without factor VIII or factor IX inhibitors

EQ-5D-5L Scores	Routine Factor-Based Prophylaxis during 6-month OP (N = 83)	Marstacimab Prophylaxis during 12-month ATP (N = 83)
Index Score		
Median Estimate (95% CI)	0.0300 (-0.0140, 0.0740)	0.0752 (0.0178, 0.1325)
Estimated Difference (95% CI)	0.0223 (-0.0432, 0.0877) Non-inferiority*	
Visual Analog Scale		
Median Estimate (95% CI)	3.0 (-0.6, 6.6)	4.5 (1.4, 7.7)
Estimated Difference (95% CI)	0.6 (-4.0, 5.1) Non-inferiority*	

*****Criterion Met (Non-inferiority/p-value if met superiority)

- Higher scores indicate better health states.
- For Index Score, the non-inferiority criterion was -0.1 (Lower Bound of difference CI >-0.1).
- For VAS score, the non-inferiority criterion was -9.5 (Lower Bound of difference CI >-9.5).
- If the non-inferiority criterion was met, superiority was to be tested per testing hierarchy.
- CI = confidence interval, OP = Observational Phase; ATP = Active Treatment Phase

Table 8 provides a comparison of the change from baseline at 6 months between prophylactic Hympavzi weekly during the Active Treatment Phase and on-demand factor-based therapy during the Observational Phase on the Physical Health Domain Score in Haem-A-QoL.

Table 8. Comparison of the change from baseline at 6 months of Haem-A-QoL Physical Health Domain Score with Hympavzi prophylaxis during ATP versus previous on-demand factor-based therapy during OP in patients ≥17 years of age without factor VIII or factor IX inhibitors

Haem-A-QoL Scores	On-Demand Factor-Based Therapy during 6-month OP (N = 31)	Hympavzi Prophylaxis during 12-month ATP (N = 31)
Physical Health Domain Score		
Median Estimate (95% CI)	-1.1 (-12.2, 10.0)	-12.4 (-19.6, -5.1)
Estimated Difference (95% CI) p-value	-10.7 (-24.0, 2.6) 0.1161	

- Haem-A-QoL scales range from 0 to 100; lower scores are reflective of better hemophilia quality of life.
- Clinically meaningful difference: Physical Health: 10 points.
- CI = Confidence Interval; OP = Observational Phase; ATP = Active Treatment Phase

Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with marstacimab. The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of marstacimab.

During the 12-month treatment period in the pivotal Phase 3 Study B7841005, 23 of the 116 (19.8%) ADA-evaluable marstacimab-treated patients developed ADAs. ADAs were transient in 61% (14/23) and persistent in 39% (9/23) of the ADA-positive patients, indicative of a transient ADA profile in the majority of the patients. ADA titres resolved in 22/23 (95.7%) patients by the end of the study. Neutralising antibodies (NAbs) developed in 6/116 (5.2%) ADA-evaluable marstacimab-treated patients during the study. The NAbs were transient in all patients and no patients were NAb positive at the end of the study. There was no identified clinically significant impact of ADAs, including NAbs, on PKs, pharmacodynamics, safety or efficacy of marstacimab over the treatment duration of 12 months. Overall, the safety profile of marstacimab was similar between those patients with ADAs (including NAbs) and those without.

In the Phase 3 OLE study, only one of the 44 ADA-evaluable patients continuing to receive marstacimab for at least 6 months was persistently positive for ADAs.

5.2 Pharmacokinetic properties

The PKs of marstacimab were determined via non-compartmental analysis in healthy participants and haemophilia A and B patients as well as using a population PK analysis on a database composed of 213 participants (150 haemophilia patients and 63 healthy participants) who received once weekly subcutaneous (30 mg to 450 mg) or intravenous (150 and 440 mg) doses of marstacimab.

Marstacimab exhibited non-linear PKs with systemic exposure to marstacimab, as measured by AUC and C_{max}, increasing in a greater than dose-proportional manner. This non-linear PK behaviour is caused by target-mediated drug disposition (TMDD) and concentration dependent non-linear elimination of marstacimab which occurs when marstacimab binds to endothelial

TFPI.

Mean steady-state accumulation ratio for marstacimab was approximately 3 to 4, relative to the first dose exposure following weekly subcutaneous dosing of 150 mg and 300 mg. Steady-state concentrations of marstacimab are expected to be achieved by approximately 60 days, i.e., by the 8th or 9th subcutaneous dose when administered once weekly. For marstacimab 150 mg subcutaneous once weekly, population estimates of mean $C_{min,ss}$, $C_{max,ss}$, and $C_{avg,ss}$ for adults and adolescents are shown in Table 9.

Table 9. Steady-state marstacimab plasma concentrations following once-weekly subcutaneous administration of 150 mg (with a loading dose of 300 mg subcutaneous)

Parameter	Adults	Adolescents
$C_{min,ss}$ (ng/mL)	13,700 (90.4%)	27,300 (53.2%)
$C_{max,ss}$ (ng/mL)	17,900 (77.5%)	34,700 (48.5%)
$C_{avg,ss}$ (ng/mL)	16,500 (81.2%)	32,100 (49.5%)

Data are presented as arithmetic mean (%CV).

$C_{min,ss}$ = minimum plasma concentration at steady state; $C_{max,ss}$ = maximum plasma concentration at steady state; $C_{avg,ss}$ = average plasma concentration at steady state

Absorption

Following multiple subcutaneous administrations of marstacimab to haemophilia patients, median T_{max} ranged from 23 to 59 hours. Bioavailability of marstacimab following subcutaneous administration was estimated to be about 68% by population PK modelling. No relevant differences were seen in marstacimab bioavailability between arm, thigh and abdomen.

Distribution

Marstacimab steady-state volume of distribution in haemophilia patients was 7.8 L based on a population PK analysis. This limited extravascular distribution suggests that marstacimab is restricted to the intravascular space.

Metabolism

Metabolism studies were not conducted with marstacimab. 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 TMDD, marstacimab is expected to be also cleared by target-mediated clearance as formation of marstacimab/TFPI complex.

Excretion

Excretion studies were not conducted with marstacimab. Based on the molecular weight, marstacimab is expected to undergo catabolic degradation and is not expected to be renally cleared. Marstacimab is cleared via linear and non-linear mechanisms. Following multiple subcutaneous doses and based on a population PK analysis, marstacimab linear clearance was approximately 0.021 L/hr. Mean effective steady-state half-life of marstacimab was estimated to be approximately 10 to 17 days for both adults and adolescents and across dose groups.

Body weight, age group, race, and haemophilia type

Although weight was an important covariate to describe the PKs of marstacimab, there is no recommended dose adjustment for weight in patients weighing >35 kg. Marstacimab clearance (CL/F) was 32% lower in adolescents (12 to <18 years of age) compared to adults (18 years and older). After adjusting for weight, CL (L/hr/kg) in adolescents was estimated to be approximately 5% lower compared to that in adults, indicating that weight accounts for most of the differences in CL. This difference in PK did not translate to a clinically relevant difference in levels of the downstream pharmacodynamic marker peak thrombin between the 2 groups.

The impact of race and haemophilia type on the PKs of marstacimab was not found to be clinically relevant in the patient population.

Clinical studies of marstacimab did not include a sufficient number of patients aged 65 years and older to determine whether there are differences in exposure compared with younger patients.

Renal impairment

Renal clearance is not considered important for elimination of mAbs due to their large size and inefficient filtration through the glomerulus. Clinical studies have not been conducted to evaluate the effect of renal impairment on the PK of marstacimab.

All patients with haemophilia A and B in the population PK analysis had normal renal function (N = 128; eGFR ≥90 mL/min/1.73 m^2) or mild renal impairment (N = 22; eGFR of 60 to 89 mL/min/1.73 m^2). Mild renal impairment did not affect the PKs of marstacimab. There are no data available on the use of marstacimab in patients with moderate or severe renal impairment.

Hepatic impairment

Clinical studies have not been conducted to evaluate the effect of hepatic impairment on the PK of marstacimab, as it is generally not considered clinically relevant for mAbs.

All patients with haemophilia A and B in the clinical studies had normal hepatic function (N = 135; total bilirubin and AST ≤ULN) or mild hepatic impairment (N = 15; total bilirubin 1× to ≤1.5× ULN or AST >ULN). Mild hepatic impairment did not affect the PKs of marstacimab. No data are available on the use of marstacimab in patients with moderate or severe hepatic impairment.

5.3 Preclinical safety data

Genotoxicity

No genotoxicity studies have been conducted with marstacimab. As a large protein molecule, marstacimab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

No carcinogenicity studies have been conducted with marstacimab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Disodium edetate
- Histidine
- Histidine hydrochloride monohydrate
- Polysorbate 80
- Sucrose
- Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C). Do not freeze. Do not shake. Keep the prefilled pen in its original carton in order to protect from light.

Hympavzi may be removed from refrigerated storage and may be stored in its original carton for one single period of maximum 7 days at room temperature (up to 30°C). The product must not be returned to refrigerated storage. Prior to the end of this period of room temperature storage, the product must be used or discarded.

6.5 Nature and contents of 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).

Each prefilled pen contains 1 mL solution for injection.

6.6 Special precautions for disposal

The product is for single use in one patient only. Discard any residue.

Do not shake.

For a more comfortable injection, allow the product to warm up to room temperature in the carton for about 15 to 30 minutes protected from direct sunlight.

Inspect the solution visually prior to use. Hympavzi is a clear and colourless to light yellow solution. Do not use if the medicine is cloudy, dark yellow, or contains flakes or particles.

Hympavzi does not contain preservatives; therefore, unused portions should be discarded. Do not use beyond expiration date.

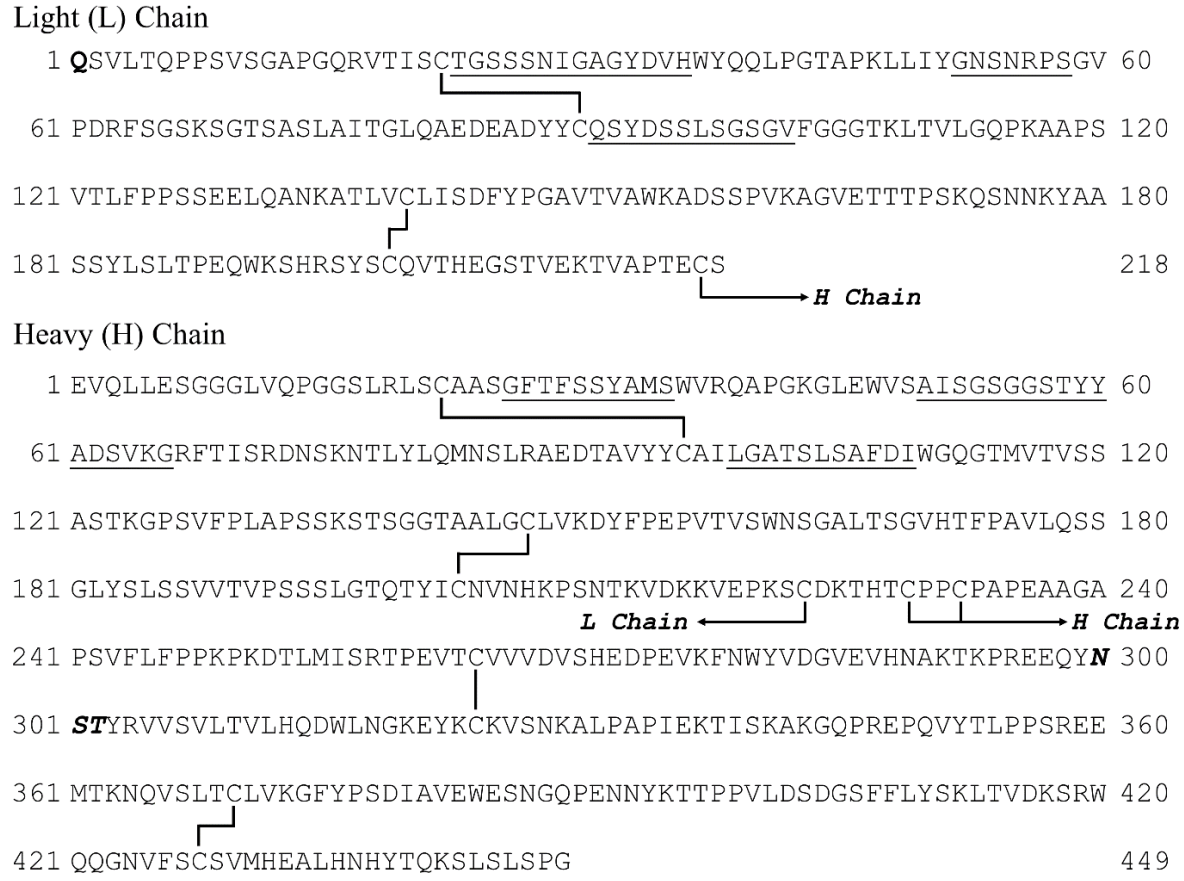
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Structure

Marstacimab is an IgG1 lambda monoclonal antibody (mAb) with two identical heavy (H) chains and two identical light (L) chains, covalently linked with four inter-chain disulfide bonds. Complete, confirmed amino acid sequence of marstacimab is shown in Figure 1. The N-terminus of the L chain is mainly pyroglutamic acid (pQ), which is known to spontaneously form in mAbs when the N-terminal residue is Q. The H chain includes three 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.

Figure 1. Marstacimab primary structure (amino acid sequence)



CAS number

1985638-39-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

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9. DATE OF FIRST APPROVAL

xx xxx xxxx

10. DATE OF REVISION

Not applicable.

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