SUMMARY OF PRODUCT CHARACTERISTICS

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare ▼ professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Hympavzi 150 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe 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

Hympavzi contains 0.2 mg polysorbate 80 in each mL of solution.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless to light yellow solution with pH of 5.8, and osmolarity of approximately 324 mOsm/L.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hympavzi is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with:

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

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a healthcare professional experienced in the treatment of haemophilia. Treatment should be initiated in a non-bleeding state.

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, at any time of day.

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. The maximum weekly dose of 300 mg should not be exceeded.

Guidance on treating breakthrough bleeds
Additional doses of Hympavzi should not be used to treat breakthrough bleeding events. For guidance on treatment in the event of breakthrough bleeds, see section 4.4.

Management in patients with acute severe illness
In acute severe illnesses with increased tissue factor expression, such as infection, sepsis, and crush injuries, potentiation of the inflammatory response via concomitant tissue factor pathway inhibitor (TFPI) inhibition could pose a risk of adverse reactions, especially thrombosis (see section 4.4).

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. Additional monitoring for adverse reactions and the development of thromboembolism may be warranted in these patients when marstacimab is administered. Hympavzi should be temporarily interrupted if clinical symptoms, imaging, and/or laboratory findings consistent with thrombotic events occur, and managed as clinically indicated. Hympavzi therapy may be resumed once the patient has clinically recovered at the clinical judgement of the healthcare provider (see Missed dose section below).

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 or 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 study data are available to guide converting patients from non-factor-based medicinal products to marstacimab. 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.

Special populations

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

Elderly
No dose adjustments are recommended in patients over 65 years of age (see section 5.2).

Paediatric population

Hympavzi should not be used in children less than 1 year of age because of potential safety issues. The safety and efficacy of marstacimab 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 marstacimab 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, it is recommended to discontinue Hympavzi 6 to 12 days prior and initiate management 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. The product information for the clotting factor concentrate should be consulted for dose 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 medicinal products (see Missed dose section above).

Method of administration

Hympavzi is for subcutaneous use 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 with the medicinal product if a 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 about 15 to 30 minutes away from direct sunlight (see sections 6.4 and 6.6). The medicinal product should not be warmed by using a heat source such as hot water or a microwave.

The recommended injection sites are the abdomen (at least 5 cm away from the navel) and thigh. Other locations are acceptable if required. Administration of Hympavzi in the upper arm (pre-filled syringe only) and buttocks (pre-filled pen only) should be performed by a caregiver or healthcare professional only. The medicinal product 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.

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 injected into a vein or muscle.

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

For comprehensive instructions on the administration of the medicinal product, see section 6.6 and the ‘Instructions for Use’ provided at the end of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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. Venous thrombotic events, including embolism, were reported in clinical studies with marstacimab (see section 4.8).

These events occurred in individuals with multiple risk factors for thromboembolism. 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), patients with prolonged periods of immobilisation, obesity, and smoking,
- patients currently experiencing an acute severe illness with increased tissue factor expression (such as serious infection, sepsis, trauma, crush injuries, cancer).

Marstacimab has not been studied in patients with a history of previous thromboembolic events (see section 5.1) and there is limited experience in patients with acute severe illness.

The use of other anti-tissue factor pathway inhibitor (anti-TFPI) products has been associated with the development of thromboembolic complications in patients exposed to additional haemostatic agents (i.e. bypassing agents) in close proximity. Factor VIII and factor IX products have been safely administered for the treatment of breakthrough bleeds in patients receiving marstacimab. If factor VIII or factor IX products are indicated in a patient receiving Hympavzi prophylaxis, the minimum effective dose of factor VIII or factor IX product according to the product label is recommended.

The benefit and risk of using Hympavzi in patients with a history of thromboembolic events, with known risk factors for thromboembolism, or currently experiencing an acute severe illness should be considered. Patients at risk should be monitored for early signs of thrombosis, and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care. Hympavzi prophylaxis should be interrupted if diagnostic findings consistent with thromboembolism occur and manage as clinically indicated.

Guidance on treating breakthrough bleeds

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. Healthcare professionals should refer to the product information for the clotting factor concentrate being used.

Hypersensitivity reactions

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

Patient with factor inhibitor

In an ongoing clinical study outside the approved indication, in haemophilia patients with inhibitors treated with marstacimab, 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.

Effects of marstacimab on coagulation tests

Marstacimab therapy does not produce clinically meaningful changes in standard measures of coagulation including activated Partial Thromboplastin Time (aPTT) and Prothrombin Time (PT).

Excipients

Polysorbate content
This medicinal product contains polysorbate 80. Polysorbate 80 may cause hypersensitivity reactions.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per 1 mL, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical drug interaction studies with marstacimab have been conducted.

As a monoclonal antibody (mAb), marstacimab is expected to be cleared through catabolic pathways. Thus an impact on its clearance via an interaction with concomitant medicinal products cleared via non-catabolic pathways is 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

Women of childbearing potential

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

Pregnancy

There are no clinical studies of marstacimab use in pregnant women. Animal reproduction studies have not been conducted with marstacimab. It is not known whether Hympavzi can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. Hympavzi should be used during pregnancy only if the potential benefit for the mother outweighs the risk to the foetus taking into account that, during pregnancy and after parturition, the risk for thrombosis is increased and that several pregnancy complications are linked to an increased risk for disseminated intravascular coagulation (DIC).

Breast-feeding

It is not known whether marstacimab is excreted in human milk. No studies have been conducted to assess the impact of marstacimab on milk production or its presence in

breast milk. Human IgG is known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, marstacimab could be used during breast-feeding if clinically needed.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3). No fertility data are available in humans. Thus, the effect of marstacimab on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

Hympavzi has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of marstacimab is based on data from clinical studies. The most serious adverse drug reaction reported from the clinical studies with marstacimab was thrombosis (0.9%) (see section 4.4).

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

Tabulated list of adverse reactions

Safety data in Table 1 are based on pooled data from the Phase 3 safety and efficacy study (BASIS) and its open-label extension (OLE) study (see section 5.1). The data from the pivotal Phase 3 study 12-month Active Treatment Phase reflects exposure of 116 male patients with haemophilia A or B without inhibitors to marstacimab 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). At the time of data cut-off, 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 reactions reported in patients who received marstacimab prophylaxis. The adverse reactions listed in the table below are presented by system organ class (SOC) and frequency categories, defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) or frequency not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1. Adverse reactions

• System organ class	• Adverse reaction	• Frequency

• Nervous system disorders	• Headache	• Common
• Vascular disorders	• Hypertension • Thromboembolic events (thrombosis[b])	• Common • Uncommon
• Skin and subcutaneous tissue disorders	• Pruritus • Rash[a]	• Common • Uncommon
• General disorders and administrations site conditions	• Injection site reactions[a]	• Very common

a. see 'Description of selected adverse reactions'
b. ADR reported in the open-label extension study post-data cut-off.

Description of selected adverse reactions

Injection site reactions
In total, 11.2% of patients treated with marstacimab reported ISRs. The majority of ISRs observed in marstacimab clinical studies were transient and reported as mild to moderate in severity. No occurrences of injection site reaction led to a dose adjustment or drug discontinuation. ISRs include injection site bruising, injection site erythema, injection site haematoma, injection site induration, injection site oedema, injection site pain, injection site pruritus, and injection site swelling.

Rash
In the non-inhibitor population, 0.9% of patients reported non-serious rash (Grade 1).

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is limited experience with overdose of marstacimab.

No serious adverse events occurred in a small number of adult patients weighing ≥ 50 kg who had up to 3 months of exposure to marstacimab at 450 mg administered subcutaneously weekly during early phase studies. However, this was a small group, and the effect of longer-term high exposures is unknown. Receiving higher doses than recommended may result in hypercoagulability.

Patients who receive an accidental overdose should immediately contact their healthcare provider and be monitored closely. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse

reactions and/or hypercoagulability and appropriate symptomatic treatment be instituted immediately.

Paediatric population

Doses in excess of 150 mg per week for adolescents aged 12 to 17 years weighing < 50 kg have not been studied. No case of overdose has been reported in the paediatric population. The principles described above apply to the management of overdose in the paediatric population.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics, other systemic hemostatics, ATC code: B02BX11

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. TFPI initially binds to and inhibits the factor Xa active site via its second Kunitz inhibitor domain (K2). The action of marstacimab to neutralise the inhibitory activity of TFPI may serve to enhance the extrinsic pathway and bypass deficiencies in the intrinsic pathway of coagulation by increasing free factor Xa available to increase thrombin generation and promote haemostasis.

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. Sporadic or transient increases in D-Dimer and prothrombin fragments 1+2 above physiological values were reported in the Phase 3 study with no associated safety concerns.

Clinical efficacy and safety

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)

The pivotal Phase 3 study 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 without FVIII inhibitors or severe haemophilia B 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 (ABRs) were 39.86 and 7.90 in a 6-month 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 the 6-month Observational Phase in which patients received either on-demand or routine prophylactic factor-based replacement 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).

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

Table 2. Comparison of ABR with Hympavzi 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)**	**Hympavzi prophylaxis during 12-month ATP (N = 83)**
Treated bleeds (Primary)		
ABR, model-based (95% CI)	7.90 (5.14, 10.66)	5.09 (3.40, 6.78)
Difference vs. RP (95% CI)	-2.81 (-5.42, -0.20) p-value = 0.0349*	
Patients with 0 bleeds, n (%)	33 (39.8)	29 (34.9)
Spontaneous bleeds, treated		
ABR, model-based (95% CI)	5.89 (3.57, 8.22)	3.78 (2.25, 5.31)
Difference vs. RP (95% CI)	-2.11 (-4.26, 0.03) Non-inferiority*	
Joint bleeds, treated		
ABR, model-based (95% CI)	5.69 (3.36, 8.02)	4.13 (2.59, 5.67)
Difference vs. RP (95% CI)	-1.55 (-3.73, 0.62)	

	Non-inferiority*	
Total bleeds, treated and untreated		
ABR, model-based (95% CI)	8.90 (6.02, 11.77)	5.98 (4.14, 7.82)
Difference vs. RP (95% CI)	-2.91 (-5.66, -0.17) Non-inferiority*	
Target joint bleeds, treated		
ABR, model-based (95% CI)	3.37 (1.60, 5.15)	2.51 (1.26, 3.76)
Difference vs. RP (95% CI)	-0.87 (-2.42, 0.69) 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 International Society on Thrombosis and Haemostasis (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

Study B7841007 interim analysis

In the 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.

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 3.

Table 3. ABR with Hympavzi 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)	4.96 (3.67, 6.70)	3.26 (2.39, 4.44)	2.79 (1.90, 4.10)
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

Immunogenicity

During the 12-month Active Treatment Phase 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. Although slightly lower mean marstacimab concentrations (approximately 24%-32% lower) were reported in ADA-positive patients compared to ADA-negative patients, concentrations largely overlapped between these 2 groups and there was no identified clinically significant effect of ADAs, including NAbs, on 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Hympavzi in one or more subsets of the paediatric population in the treatment of congenital haemophilia A and congenital haemophilia B.

5.2 Pharmacokinetic properties

The pharmacokinetics of marstacimab were determined via non-compartmental analysis in healthy participants and haemophilia A and B patients as well as using a population pharmacokinetic 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 pharmacokinetics with systemic exposure to marstacimab, as measured by AUC and C_{max}, increasing in a greater than dose-proportional manner. This non-linear pharmacokinetic 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 8^{th} or 9^{th} subcutaneous dose when administered once weekly. For marstacimab 150 mg subcutaneous once weekly, population estimates of mean $C_{max,ss}$, $C_{min,ss}$, and $C_{avg,ss}$ for adults and adolescents are shown in Table 4.

Table 4. 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 71% by population pharmacokinetic modeling. No relevant differences were seen in marstacimab bioavailability between arm, thigh and abdomen.

Distribution

Marstacimab steady-state volume of distribution in haemophilia patients was 8.6 L based on a population pharmacokinetic analysis. This limited extravascular distribution suggests that marstacimab is restricted to the intravascular space.

Biotransformation

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.

Elimination

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 0.019 L/hr. Mean effective steady-state half-life of marstacimab was estimated to be approximately 16 to 18 days for both adults and adolescents and across dose groups.

Special populations

Body weight, age group, race, and haemophilia type
Although weight was an important covariate to describe the pharmacokinetics of marstacimab, no alteration in dosing is required based on weight in patients weighing ≥ 35 kg. Marstacimab clearance (CL) was 29% 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 3% 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 haemophilia type on the pharmacokinetics of marstacimab was not found to be clinically relevant in the patient population.

Race (Asian vs. non-Asian) was not identified as a covariate influencing marstacimab pharmacokinetics. Marstacimab weight-adjusted clearance was 32% higher in Asian patients as compared to non-Asian patients. This difference is not considered clinically relevant. There are insufficient data to evaluate potential differences in the exposure of marstacimab in other races or ethnicity.

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 pharmacokinetic analysis had normal renal function (N = 129; eGFR ≥ 90 mL/min/1.73 m^2) or mild renal impairment (N = 21; eGFR of 60 to 89 mL/min/1.73 m^2). Mild renal impairment did not affect the pharmacokinetics of marstacimab. There are no data available on the use of marstacimab in patients with moderate or severe renal impairment.

Marstacimab is a monoclonal antibody and is cleared via catabolism rather than renal excretion and a change in dose is not expected to be required for patients with 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). Mild hepatic impairment did not affect the pharmacokinetics of marstacimab. No data are available on the use of marstacimab in patients with moderate or severe hepatic impairment.

Marstacimab is a monoclonal antibody and is cleared via catabolism rather than hepatic metabolism and a change in dose is not expected to be required for patients with hepatic impairment.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on repeat-dose toxicity, including safety pharmacology endpoints, and local tolerance. Reversible mixed cell infiltration, haemorrhage, and necrosis were observed at the injection sites in rats following subcutaneous injection. No studies have been conducted to assess the potential for carcinogenicity, mutagenicity, or effects on embryo-foetal development.

Impairment of fertility

Marstacimab did not affect fertility or early embryonic development when administered as a repeat dose to male rats at doses up to 1 000 mg/kg/dose and an exposure margin of 212× the AUC exposure at a clinical dose of 300 mg subcutaneous weekly.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
L-Histidine
L-Histidine monohydrochloride
Polysorbate 80 (E 433)
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

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C). Do not freeze. Keep the pre-filled syringe or pre-filled pen in its original carton in order to protect from light.

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

6.5 Nature and contents of container

Each carton contains one single-dose pre-filled syringe (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 pre-filled syringe contains 1 mL solution for injection.

6.6 Special precautions for disposal

This medicinal product is for single use only.

Do not shake.

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

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

Comprehensive instructions for the preparation and administration of the medicinal product are provided in the package leaflet and ‘Instructions for Use’.

Hympavzi does not contain preservatives; therefore, unused portions should be discarded.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00057/1730

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

18/02/2026