swissmedic

Date: 20 February 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Hympavzi

International non-proprietary name: marstacimab
Pharmaceutical form: solution for injection in pre-filled pen
Dosage strength(s): 150 mg/1 mL
Route(s) of administration: subcutaneous
Marketing authorisation holder: Pfizer AG
Marketing authorisation no.: 69556
Decision and decision date: approved on 23 December 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for marstacimab in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 14 November 2023.

Work-sharing procedure
The applicant requested a work-sharing procedure with Singapore and Australia.
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), and Swissmedic – and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

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.

2.2.2 Approved indication

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.

2.2.3 Requested dosage

Summary of the requested standard dosage

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.

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 physician/healthcare professional. There are insufficient data to recommend doses above 300 mg weekly.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	1 February 2024
Formal control completed	1 March 2024
List of Questions (LoQ)	1 July 2024
Response to LoQ	27 August 2024
2nd List of Questions (LoQ II)	28 October 2024
Response to LoQ II	11 November 2024
Preliminary decision	27 November 2024
Response to preliminary decision	12 December 2024
Final decision	23 December 2024
Decision	approval

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant’s request / Work-sharing procedure).

4 Nonclinical aspects

The nonclinical development programme for Hympavzi, containing the new active substance marstacimab, followed relevant ICH guidelines. The pivotal safety studies were performed in compliance with GLP regulations.

4.1 Pharmacology

Marstacimab bound to TFPI K1K2 human, rat, and cynomolgus monkey tissue factor pathway inhibitor (TFPI) with affinities (K_D) of 3.7, 1.57, and 1.22 nM, respectively. Marstacimab bound to Kunitz domain 2 (K2) of human TFPI with a K_D of 2.63 nM and did not bind to Kunitz domain 1 (K1).

In vitro, marstacimab neutralised TFPI inhibition of factor Xa or of FVIIa/TF-mediated FX activation with EC_{50}s of 8.75 nM and 13.23 nM, respectively. In thromboelastography experiments marstacimab at 0.11 nM to 213 nM neutralised TFPI in whole blood from healthy non-haemophilic donors and accelerated clot formation by decreasing clotting time and clot formation time in a concentration-dependent manner. In the thrombin generation assay (TGA), the diluted prothrombin time (dPT) assay, and the activated partial thromboplastin time (aPTT) assay, marstacimab shortened the dPT clotting time in non-haemophilic human and cynomolgus monkey plasma with EC_{50}s of 2.7 nM and 1.7 nM, respectively, without affecting the aPTT time. The pro-haemostatic impacts of marstacimab were similarly demonstrated when tested with haemophilic human plasma samples.

In vivo, pharmacological effect was evidenced in cynomolgus monkeys following a single subcutaneous (SC) 3 mg/kg dose of marstacimab by decreased dPT time and increased TFPI concentration. In haemophilic mouse injury models, including the acute tail clip injury model and the laser induced injury model, administration of a single intravenous (IV) dose to haemophilia A (FVIII deficient) and B (FIX deficient) mice up to 6 mg/kg pre-bleeding reduced blood loss. The animals remained protected from bleeding for a minimum of 189 hours (haemophilia A mice) and 72 hours (haemophilia B mice). Additionally, enhanced platelet accumulation and fibrin deposition at the injury site were observed in haemophilic mice compared to non-haemophilic animals. Marstacimab restored haemostasis in haemophilia mouse injury models when administered before and after the onset of a bleeding injury.

The Fc triple mutation of marstacimab was demonstrated to effectively diminish Fc effector function. Marstacimab did not bind to C1q or FcγR at doses up to 0.207 µM, suggesting low potential of inducing complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC).

No marstacimab-related effects on the cardiovascular, central nervous, and respiratory systems were observed in monkeys at clinically relevant doses.

The pharmacodynamic drug interaction potential and pharmacokinetic drug interaction (DDI) of marstacimab with authorised bypassing agents were evaluated both *in vitro* in human haemophilia plasma and *in vivo* in rats. The effects of marstacimab in combination with these agents were consistent with the expected pharmacology and remained within the physiological range.

Pharmacodynamic studies demonstrated that marstacimab specifically bound to TFPI K1K2 and identified rats and cynomolgus monkeys as relevant nonclinical species. The data support the use of marstacimab as an antibody against TFPI for prophylactic treatment of haemophilia A and B.

4.2 Pharmacokinetics

The pharmacokinetic (PK) profile of marstacimab following SC administration in male rats and cynomolgus monkeys exhibited dose-dependent increases in C_{max} and AUC. The time to reach maximum concentration (T_{max}) ranged from 2 to 72 hours in both species (compared to patients: T_{max} = 23 to 53 hours). Monkeys displayed a half-life ($t_{1/2}$) ranging from 36.5 to 163 hours. Bioavailability in rats was approximately 70%. Overall, nonclinical PK parameters were considered comparable to humans. Toxicokinetic data indicated no sex-related differences and showed increased systemic exposure with escalating doses. Exposure increased in monkeys after repeated dosing. This observation aligns with the finding that the total TFPI concentration increased with rising plasma levels

of marstacimab and decreased upon marstacimab elimination. Thus, marstacimab exhibited a target-mediated drug disposition (TMDD) in cynomolgus monkeys, supporting its binding to the target.

In accordance with ICH S6(R1), studies on metabolism or excretion were not conducted.

Marstacimab resulted in the development of anti-drug antibodies (ADA) following repeated dosing in rats, without effects on exposure. ADA development was not observed in monkeys.

4.3 Toxicology

The toxicological profile of marstacimab was characterised in repeat-dose toxicology studies in cynomolgus monkeys for up to 3 months and rats for up to 6 months. These studies, conducted in accordance with ICH S6(R1), evaluated both IV and SC routes of administration, supporting the intended SC clinical route, dosing frequency, and treatment duration. Doses of up to 500 mg/kg (IV) and 90 mg/kg (SC) were administered once weekly to cynomolgus monkeys and up to 1000 mg/kg (IV) and 180 mg/kg (SC) to rats. Repeated dosing of marstacimab resulted in effects on the coagulation cascade, including prolonged prothrombin time, decreased fibrinogen, and increased D-dimer concentrations, confirming its pharmacological activity. No adverse effects were observed in cynomolgus monkeys up to the highest SC dose (90 mg/kg), which based on the AUC is 30 times higher than human exposure to marstacimab at the maximum recommended human dose (MRHD). In rats, marstacimab-related microscopic findings were noted at ≥ 60 mg/kg (AUC ≥ 5.8 times higher than clinical exposure at MRHD). These findings included minimal thrombi/emboli (both acute and organising) and minimal cellular infiltrate with refractile material of unknown origin in the lung. The thrombi/emboli correlated with clinical pathology findings in coagulation parameters and the presence of this material, which is likely the cause of the thrombi/emboli formation. Given the minimal nature of these findings and the absence of adverse secondary effects, they were considered nonadverse and attributed to the exaggerated pharmacology of marstacimab. Nevertheless, thromboembolic events were identified as an important potential risk and mentioned in the Information for healthcare professionals.

In accordance with ICH S6(R1), no genotoxicity studies were conducted.

No carcinogenicity studies were performed. In line with ICH S6(R1), the applicant conducted a carcinogenicity assessment utilising a weight of evidence approach. Marstacimab is not anticipated to pose a carcinogenic risk to patients.

The reproductive and developmental safety profile of marstacimab was evaluated in a single study focused on male fertility and early embryonic development in rats. This study design was considered appropriate given the X-linked nature of haemophilia and its low prevalence in women. Marstacimab was well tolerated, with no observed effects on male fertility and embryonic survival. The NOAEL was 1000 mg/kg, corresponding to systemic exposure 370 times higher than clinical exposure, based on plasma C_{max}. Knockout studies have shown TFPI as critical for development, with inactivation of the TFPI gene in mice resulting in embryofetal lethality. The implications of TFPI blockade in pregnancy remain unclear, and marstacimab is not recommended for use during pregnancy, as addressed in the Information for healthcare professionals.

When comparing to the clinical AUC value of 12,100 µg·h/mL, the systemic AUC-based exposures at the NOAEL of 90 mg/kg following SC administration in monkeys and of 1000 mg/kg after IV administration in rats were determined to be 30- and 152-times higher than clinical exposure. These values represent large multiples of the predicted human therapeutic exposure in haemophilic patients.

Marstacimab showed a low potential for irritation following SC administration in a dedicated study in rats and in the repeat-dose toxicity studies in rats and cynomolgus monkeys. However, in the clinical studies, injection site reactions were frequently reported.

Mastacimab demonstrated no relevant cytokine release potential *in vitro*. Specifically, it did not induce cytokine release (TNF-α, IL-6, or IFN - γ) at concentrations up to 6.9 µM. Furthermore, no evidence of immunosuppression or immunostimulation was noted in the repeat-dose toxicity studies conducted in cynomolgus monkeys and rats. Overall, the immunotoxic potential of marstacimab is considered low.

There are no safety concerns regarding excipients and impurities.

Based on the ERA, there is no particular risk for the environment.

The RMP adequately addresses the nonclinical findings and their relevance for clinical use.

No specific studies in juvenile animals have been conducted with marstacimab. Nonclinical studies were not foreseen in the PIP agreed by the EMA/PDCO for the paediatric population from 1 year to less than 18 years of age.

4.4 Nonclinical conclusions

In conclusion, the pharmaco-toxicological profile of marstacimab is considered to be sufficiently well characterised. The submitted nonclinical data support the approval of Hympavzi in the proposed indication. The relevant information has been included in the Information for healthcare professionals.

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's request / Work-sharing procedure).

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Hympavzi was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

Hympavzi 150 mg solution for injection in pre-filled pen

Composition

Active substances

Marstacimabum (produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells).

Excipients

Dinatrii edetas, L-histidinum, L-histidini hydrochloridum monohydricum, polysorbatum 80, saccharum, aqua ad iniectabile q.s. ad solutionem pro 1 ml.

Sodium content: 0.0062 mg per pre-filled pen.

Pharmaceutical form and active substance quantity per unit

Solution for injection in pre-filled pen for subcutaneous injection.

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

Solution for injection in pre-filled pen: Each pre-filled pen contains 150 mg marstacimab in 1 ml of solution.

Indications/Uses

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

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

Dosage/Administration

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

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

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 physician/healthcare professional. The maximum weekly dose of 300 mg should not be exceeded.

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 hemophilia 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 labeled half-life before initiating treatment with Hympavzi. Hemostatic support with clotting factor concentrates may be needed during the switch from other non-factor-based hemophilia medicinal products to Hympavzi.

Special dosage instructions

Guidance on use with breakthrough bleed treatments

Additional doses of Hympavzi should not be used to treat breakthrough bleeding events.

Factor VIII and factor IX products can be administered for the treatment of breakthrough bleeds in patients receiving Hympavzi. Physicians/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 «Warnings and precautions»). Please refer to the product information for the clotting factor concentrate being used.

Patients with hepatic disorders

No dose adjustments are recommended in patients with mild hepatic impairment (see «Pharmacokinetics»). Marstacimab has not been studied in patients with moderate or severe hepatic impairment.

Patients with renal disorders

No dose adjustments are recommended in patients with mild renal impairment (see «Pharmacokinetics»). Marstacimab has not been studied in patients with moderate or severe renal impairment.

Elderly patients

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

Children and adolescents

Hympavzi should not be used in children less than 1 year of age because of potential safety issues. The safety and efficacy of Hympavzi in pediatric patients <12 years of age have not yet been established. The safety and efficacy of Hympavzi 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 6 to 12 days prior surgery 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 hemophilia 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 hemostatic products and other concomitant medications (see «Missed dose» above).

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 «Warnings and precautions»).

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. 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. These should be managed as clinically indicated. Hympavzi therapy can be resumed once the patient has clinically recovered at the clinical judgement of the healthcare provider (see «Missed dose» above).

Mode of administration

Hympavzi is for subcutaneous injection only.

Hympavzi is intended for use under the guidance of a physician/healthcare professional. After proper training in subcutaneous injection technique, a patient or caregiver may inject with 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 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 «Other information»).

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 or muscle.

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

Refer to the Patient Information - Instructions for Use for complete administration instructions.

Contraindications

Hypersensitivity to marstacimab or to any of the excipients (see «Composition»).

Warnings and precautions

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 «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 (see «Properties/Effects») 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 in patients exposed to additional haemostatic agents in close proximity. 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 or factor IX product according to the product label is recommended.

Consider the benefit and risk of using Hympavzi in patients with known risk factors for thromboembolism. 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.

Hypersensitivity reactions

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

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).

Polysorbate content

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

Excipients of particular interest

This medicinal product contains less than 1 mmol sodium (23 mg) in each pre-filled pen, i.e. it is almost «sodium free».

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 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.

Pregnancy, lactation

Women of childbearing potential

Women of childbearing potential receiving Hympavzi have to use effective contraception during the therapy, and up to 12 weeks after cessation of Hympavzi treatment (see «Pharmacokinetics»).

Pregnancy

There are no data from the use of marstacimab in pregnant women. No animal studies have been conducted with marstacimab. The use of Hympavzi during pregnancy and in women of childbearing age not using contraception is not recommended. 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).

Lactation

It is unknown whether marstacimab is excreted in human milk. Lactation studies have not been conducted in humans or animals. Human IgG is known to be present in human milk. A risk for the breast-fed infant cannot be excluded. A decision must be made whether to discontinue breast-feeding

or to abstain from Hympavzi therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of marstacimab on human fertility has not been studied. Animal studies have not shown impairment of male fertility.

Effects on ability to drive and use machines

No corresponding studies have been performed. Hympavzi has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

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

List of undesirable effects

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-center study was conducted in adolescent and adult patients with severe (coagulation factor activity <1%) hemophilia A or B between ages 12 to <75 years without inhibitors comparing factor-based therapy to Hympavzi prophylaxis (see «Properties/Effects»). The data from the Phase 3 study 12-month active treatment phase reflects exposure of 116 male patients with hemophilia 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).

Summarized below are the adverse drug reactions reported in patients who received Hympavzi prophylaxis. The adverse reactions 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).

Nervous system disorders

Common: Headache.

Vascular disorders

Common: Hypertension.

Uncommon: Thrombosis.

Skin and subcutaneous tissue disorders

Common: Pruritus.

Uncommon: Rash.

General disorders and administration site conditions

Very common: Injection site reactions (11.2%, including injection site bruising, injection site erythema, injection site haematoma, injection site induration, injection site oedema, injection site pain, injection site pruritus, injection site swelling).

Description of specific adverse reactions and additional information

Thromboembolic events

One patient with hemophilia A developed a deep vein thrombosis after approximately 3 years of Hympavzi exposure, Hympavzi treatment was withdrawn, and anticoagulant administered.

One healthy participant developed a deep vein thrombosis and pulmonary embolism 9 days after receiving a single dose of 300 mg Hympavzi and approximately 4 weeks after receiving a second dose of a vector-based COVID-19 vaccine. Participant received anticoagulant treatment, adverse reactions resolved, and participant permanently withdrew from the study.

Injection site reactions

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. 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, one (0.9%) patient reported non-serious rash (Grade 1).

In the inhibitor population of an ongoing clinical study in which 35 hemophilia patients with inhibitors are treated with Hympavzi, one (2.9%) patient with severe hemophilia 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.

Pediatric population

The pediatric 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.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

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.

Children and adolescents

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.

Properties/Effects

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.

Pharmacodynamics

Consistent with its anti-TFPI mechanism, marstacimab administration to hemophilia patients causes an increase in downstream biomarkers of thrombin generation such as prothrombin fragments 1+2, peak thrombin, and D-dimer. An increase in total TFPI is seen, which is consistent with binding of free TFPI with marstacimab, resulting in delayed elimination of marstacimab-bound TFPI due to the much longer half-life of marstacimab than TFPI. These changes were reversible after treatment discontinuation. Marstacimab therapy does not produce clinically meaningful changes in the standard measures of coagulation: activated partial thromboplastin time (aPTT) and prothrombin time (PT).

Clinical efficacy

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

Patients (aged ≥12 years old and a body weight of ≥35 kg) with hemophilia A without inhibitors and hemophilia B without inhibitors (Study B7841005/BASIS)

The pivotal Phase 3 study was a one-way, cross-over, open-label, multi-center study in 116 adult and adolescent males (aged ≥12 years old and a body weight of ≥35 kg) with severe hemophilia A without FVIII inhibitors or severe hemophilia 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 ischemic disease were excluded from the study.

The study population was characterized by a severe bleeding phenotype. The mean annualized bleeding rates (ABRs) 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 Hympavzi 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 Hympavzi followed by maintenance doses of 150 mg of Hympavzi once weekly for 12 months. Dose escalation to 300 mg of Hympavzi 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 Hympavzi 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% hemophilia A, 21.6% hemophilia B).

The primary efficacy objective of the study was to compare Hympavzi 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 Hympavzi 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 1 shows the efficacy results of Hympavzi prophylaxis compared with routine prophylactic factor-based therapy. Hympavzi demonstrated non-inferiority and superiority over routine prophylactic factor-based therapy as measured by ABR of treated bleeds.

Table 1 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)	7.85 (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 = Annualized Bleeding Rate; CI = Confidence Interval; OP = Observational Phase; ATP = Active Treatment Phase; RP = Routine Prophylaxis.

In a supportive analysis, Hympavzi also demonstrated superiority over on-demand factor-based therapy in incidences of treated bleeds, spontaneous bleeds, joint bleeds, total bleeds and target joint bleeds.

Interim analysis of Study B7841007

In the open-label extension 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 Hympavzi prophylaxis over time. The model-based mean and other descriptive summaries for the ABR of treated bleeds are shown in Table 2.

Table 2. Annualized bleeding rate 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)	4.95 (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 Hympavzi 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 = Annualized 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

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 titers resolved in 22/23 (95.7%) patients by the end of the study. Neutralizing 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 pharmacokinetics, 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.

Pharmacokinetics

The pharmacokinetics of marstacimab were determined via non-compartmental analysis in healthy participants and hemophilia A and B patients as well as using a population pharmacokinetic analysis on a database composed of 213 participants (150 hemophilia patients and 63 healthy participants)

who received once weekly subcutaneous (30 mg to 450 mg) or intravenous (150 mg 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 behavior 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 4 to 5, 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 3.

Table 3. 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 hemophilia 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 modelling. No relevant differences were seen in marstacimab bioavailability between arm, thigh and abdomen. Other administration sites such as the buttocks have not been studied in population pharmacokinetic modelling.

Distribution

Marstacimab steady-state volume of distribution in hemophilia patients was 8.6 l based on a population pharmacokinetic analysis.

Metabolism

Metabolism studies were not conducted with marstacimab. Similar to other therapeutic monoclonal antibodies marstacimab is expected to undergo proteolytic catabolism.

Elimination

Based on the molecular weight, marstacimab is not expected to be renally cleared. Following uptake similar to other therapeutic mAbs, marstacimab is expected to be eliminated primarily by proteolytic catabolism. Additionally, based on the TMDD, marstacimab is also expected to be cleared by target-mediated clearance as formation of marstacimab/TFPI complex. 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/h. 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.

Kinetics in specific patient groups

Body weight, age group, race, and hemophilia type

Weight is a covariate to describe the pharmacokinetics of marstacimab. In the population PK analysis, the calculated marstacimab AUC_{ss} value was on average 2.4 times higher in patients weighing 44.9 kg (5th percentile of the population studied) and on average 0.34 times lower in patients weighing 95.1 kg (95th percentile of the population studied) as compared to average AUC_{ss} at the mean weight.

Marstacimab clearance (CL/F) was 29% lower in adolescents (12 to <18 years of age) compared to adults (18 years and older), which is mainly due to differences in weight. Differences in weight-adjusted CL/F are minimal (3%). AUC_{ss} is approximately 2.5-fold higher in adolescents compared to adults.

The impact of race (Asian versus non-Asian) and hemophilia type on the pharmacokinetics of marstacimab was not found to be clinically relevant in the patient population.

The number of patients aged 65 years and over in the clinical studies was insufficient to determine whether there are differences in exposure.

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 hemophilia 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 pharmacokinetics of marstacimab. No data are available on the use of marstacimab in patients with moderate or severe hepatic impairment.

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 hemophilia 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.

Preclinical data

Preclinical data reveal no special hazard for humans based on repeat-dose toxicity studies (including safety pharmacology endpoints) and studies on male fertility.

No studies have been conducted to investigate the genotoxicity, carcinogenicity or embryo-fetal developmental toxicity of marstacimab.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the pack.

Special precautions for storage

Store in the refrigerator (2-8°C).

Do not freeze.

Do not shake.

Keep the container in the outer carton in order to protect the contents from light.

Keep out of the reach of children.

The 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 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.

Instructions for handling

The product is for single use only.

Do not shake.

For a more comfortable injection, allow the 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 medicine is cloudy, dark yellow, or contains flakes or particles.

Comprehensive instructions for the preparation and administration of the product are provided in the Patient Information - Instructions for Use.

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

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

Authorisation number

69556 (Swissmedic).

Packs

Pack with 1 pre-filled pen with 150 mg/1 ml [A].

Each carton contains one single-dose pre-filled 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).

Marketing authorisation holder

Pfizer AG, Zürich.

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