ヒムペブジ皮下注 150mg ペン

に関する資料

本資料に記載された情報に係る権利及び内容の責任は、ファイザー株式会社にあります。当該製品の適正使用の目的以外の営利目的に本資料を利用することはできません。

ファイザー株式会社

TABLE OF CONTENTS

LIST OF TABLES 1
1. 起原又は発見の経緯 2
2. 開発の経緯図 2

LIST OF TABLES

Table 1. 開発の経緯図 3

1. 起原又は発見の経緯

当該内容については、M2.5.1 を参照。

2. 開発の経緯図

開発の経緯図を Table 1 に示す。

Table 1.　開発の経緯図

本申請に含まれるすべての薬理試験と臨床試験の実施期間を記載した。

なお本申請には、品質に関する試験、薬物動態試験、毒性試験の資料は含まれない。

非臨床試験

試験項目		試験内容	2020	2021	2022	2023	2024	2025
			令和2	令和3	令和4	令和5	令和6	令和7
薬理試験	外国	効力を裏付ける試験	[redacted]					

臨床試験

試験項目		試験内容		2020	2021	2022	2023	2024	2025
				令和2	令和3	令和4	令和5	令和6	令和7
臨床試験	第3相	国内及び外国	有効性及び安全性検証試験	[redacted]					
			長期安全性，忍容性及び有効性評価試験（長期継続投与試験）						
			PK，PD，安全性，忍容性及び有効性評価試験（小児開発）						

*参考資料

マルスタシマブは 2024 年 10 月に米国で承認されて以降、2026 年 5 月時点で、欧州連合をはじめとする 58 カ国で承認されている。

また、「インヒビターを保有する先天性血友病患者」を対象とした効能又は効果の追加については、欧州連合では 2026 年 5 月、米国では 2026 年 6 月に承認されている。

外国の添付文書として米国および欧州連合の添付文書の原文・和訳、ならびに企業中核データシート（Core Data Sheet：CDS）を添付する。

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HYMPAVZI safely and effectively. See full prescribing information for HYMPAVZI.

HYMPAVZI® (marstacimab-hncq) injection, for subcutaneous use
Initial U.S. Approval: 2024

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	06/2026
Dosage and Administration (2.2, 2.5, 2.8)	06/2026
Warnings and Precautions, Increased Laboratory Values of Fibrin D-dimer and Prothrombin Fragment 1.2 (5.4)	06/2026

---------- INDICATIONS AND USAGE----------

HYMPAVZI is a tissue factor pathway inhibitor (TFPI) antagonist indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 6 years of age and older with:

- hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors, or
- hemophilia B (congenital factor IX deficiency) with or without factor IX inhibitors. (1)

----------DOSAGE AND ADMINISTRATION----------

- See Full Prescribing Information for important dosing and administration instructions. (2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8)
- Recommended Dosage in Adults and Pediatric Patients 12 Years of Age and Older:
  - Loading dose: 300 mg (two 150 mg injections) by subcutaneous injection. (2.1)
  - Maintenance dose: One week after the loading dose, initiate maintenance dosing of 150 mg every week by subcutaneous injection on the same day each week, at any time of day. (2.1)
  - Dose adjustment to 300 mg subcutaneous injection weekly can be considered. (2.1)
- Recommended Dosage in Pediatric Patients 6 to less than 12 Years of Age:
  - Loading dose: 150 mg (one 150 mg injection or two 75 mg injections) by subcutaneous injection. (2.2)
  - Maintenance dose: One week after the loading dose, initiate maintenance dosing of 75 mg every week by subcutaneous injection on the same day each week, at any time of day. (2.2)
  - Dose adjustment to 150 mg subcutaneous injection (one 150 mg injection or two 75 mg injections) weekly can be considered. (2.2)
- Factor VIII and factor IX products or bypassing agents (e.g., rFVIIa or aPCC) can be administered for the treatment of breakthrough bleeds in patients receiving HYMPAVZI. Do not use additional doses of HYMPAVZI to treat breakthrough bleeds. (2.5)
- Temporarily pause HYMPAVZI at least 7 days before major surgery. (2.6)

---------- DOSAGE FORMS AND STRENGTHS----------

- Injection: 150 mg/mL and 75 mg/0.5 mL in a single-dose prefilled syringe (3)
- Injection: 150 mg/mL and 75 mg/0.5 mL in a single-dose prefilled pen (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Thromboembolic Events: Thromboembolic events may occur. Interrupt HYMPAVZI prophylaxis if symptoms occur. (5.1)
- Hypersensitivity: Hypersensitivity reactions may occur. In the event of a severe allergic reaction, discontinue HYMPAVZI. (5.2)
- Embryofetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.3, 8.1, 8.3)
- Increased Laboratory Values of Fibrin D-dimer and Prothrombin Fragment 1.2: HYMPAVZI can cause sporadic or transient increases in fibrin D-dimer and prothrombin fragment 1.2 above physiological values. (5.4)

---------- ADVERSE REACTIONS ----------

Adverse reactions reported in ≥2% of HYMPAVZI-treated patients were injection site reaction, headache, pyrexia, arthralgia, diarrhea, pruritus, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 6/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage in Adults and Pediatric Patients 12 Years of Age and Older
2.2 Recommended Dosage in Pediatric Patients 6 to less than 12 Years of Age
2.3 Preparation and Administration
2.4 Changing to HYMPAVZI
2.5 Guidance on Use with Breakthrough Bleed Treatments
2.6 Temporary Interruption for Surgery and Other Interventions
2.7 Pregnancy Testing
2.8 Immune Tolerance Induction
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Thromboembolic Events
5.2 Hypersensitivity
5.3 Embryofetal Toxicity
5.4 Increased Laboratory Values of Fibrin D-dimer and Prothrombin Fragment 1.2
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.6 Immunogenicity
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Hemophilia A and B without Inhibitors in Adults and Pediatric Patients 12 Years of Age and Older
14.2 Hemophilia A and B with Inhibitors in Adults and Pediatric Patients 12 Years of Age and Older
14.3 Hemophilia A and B with or without Inhibitors in Pediatric Patients 6 to less than 18 Years of Age
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Recommended Storage and Handling
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HYMPAVZI is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 6 years of age and older with:

- hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors, or
- hemophilia B (congenital factor IX deficiency) with or without factor IX inhibitors.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Adults and Pediatric Patients 12 Years of Age and Older

For subcutaneous use only.
The recommended dosage of HYMPAVZI for adults and pediatric patients 12 years of age and older is as follows:

Loading Dose
300 mg (two 150 mg subcutaneous injections)

If more than one injection is required to deliver a complete dose, administer each injection at a different injection site.

Maintenance Dose
One week after the loading dose, initiate maintenance dosing of 150 mg every week by subcutaneous injection on the same day each week, at any time of day.

Dose Adjustment During Treatment
In patients weighing greater than or equal to 50 kg, consider a dose adjustment to 300 mg subcutaneous injection weekly when control of bleeding events is judged to be inadequate by the healthcare provider. Safety and efficacy of HYMPAVZI at doses above 300 mg weekly have not been established.

If more than one injection is required to deliver a complete dose, administer each injection at a different injection site.

Missed Doses
For patients on a maintenance dose of 150 mg:
If a dose is missed, administer as soon as possible before the day of the next scheduled dose, and then resume usual 150 mg subcutaneous weekly dosing schedule (same schedule as prior to the missed dose or new schedule based on date of administration of missed dose).

If more than 13 days have passed since the last dose was administered, administer a loading dose of 300 mg by subcutaneous injection followed by a resumption of 150 mg by subcutaneous injection once weekly thereafter.

For patients on a maintenance dose of 300 mg:
If one or more doses are missed, administer a dose as soon as possible, and then resume 300 mg subcutaneous weekly dosing schedule (same schedule as prior to the missed dose or new schedule based on date of administration of missed dose).

2.2 Recommended Dosage in Pediatric Patients 6 to less than 12 Years of Age

For subcutaneous use only.
The recommended dosage of HYMPAVZI for pediatric patients 6 to less than 12 years of age is as follows:

Loading Dose
150 mg (one 150 mg subcutaneous injection or two 75 mg subcutaneous injections)

If more than one injection is required to deliver a complete dose, administer each injection at a different injection site.

Maintenance Dose
One week after the loading dose, initiate maintenance dosing of 75 mg every week by subcutaneous injection on the same day each week, at any time of day.

Dose Adjustment During Treatment
In patients weighing greater than or equal to 25 kg, consider a dose adjustment to 150 mg subcutaneous injection (one 150 mg subcutaneous injection or two 75 mg subcutaneous injections) weekly when control of bleeding events is judged to be inadequate by the healthcare provider. Safety and efficacy of HYMPAVZI at doses above 150 mg weekly have not been established in children 6 to less than 12 years of age.

If more than one injection is required to deliver a complete dose, administer each injection at a different injection site.

Missed Doses
For patients on a maintenance dose of 75 mg:
If a dose is missed, administer as soon as possible before the day of the next scheduled dose, and then resume usual 75 mg subcutaneous weekly dosing schedule (same schedule as prior to the missed dose or new schedule based on date of administration of missed dose).

If more than 13 days have passed since the last dose was administered, administer a loading dose of 150 mg by subcutaneous injection followed by a resumption of 75 mg by subcutaneous injection once weekly thereafter.

For patients on a maintenance dose of 150 mg:
If one or more doses are missed, administer a dose as soon as possible, and then resume 150 mg subcutaneous weekly dosing schedule (same schedule as prior to the missed dose or new schedule based on date of administration of missed dose).

2.3 Preparation and Administration

- HYMPAVZI is intended for use under the guidance of a healthcare provider. After proper instruction in subcutaneous injection technique, a patient 12 years and older may self-inject or the patient's caregiver may administer HYMPAVZI, if a healthcare provider determines that it is appropriate.
- Refer to the Instructions for Use for complete preparation and administration instructions.
- Prior to subcutaneous administration, HYMPAVZI may be removed from the refrigerator and allowed to warm at room temperature [up to 86°F (30°C)] in the carton for 15 to 30 minutes protected from direct sunlight. Do not warm by using a heat source such as hot water or a microwave. After removal of HYMPAVZI from the refrigerator, use within 7 days or discard *[see How Supplied/Storage and Handling (16)]*.
- Administer HYMPAVZI by subcutaneous injection, once weekly, at any time of the day in the abdomen or front of thigh. Other injection sites are acceptable if required. Administration of HYMPAVZI in the back of upper arm (prefilled syringe only) or buttocks (prefilled pen only) should be performed by a

caregiver or healthcare professional only. 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. Rotate the injection site with each new injection.
- During treatment with HYMPAVZI, other medicinal products for subcutaneous administration should, preferably, be injected at different anatomical sites.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. HYMPAVZI is a clear and colorless to light yellow solution. Do not use if the solution is cloudy, dark yellow, or contains flakes or particles.

2.4 Changing to HYMPAVZI

Changing from prophylactic factor replacement therapy or bypassing agents to HYMPAVZI: Prior to initiation of HYMPAVZI, discontinue treatment with clotting factor concentrates (factor VIII or factor IX concentrates) or bypassing agents (e.g., recombinant FVIIa [rFVIIa] or activated prothrombin complex concentrate [aPCC]). HYMPAVZI can be initiated at any time after discontinuing clotting factor concentrates or bypassing agents.

No data are available in patients changing from other non-factor-based hemophilia medicinal products to HYMPAVZI.

2.5 Guidance on Use with Breakthrough Bleed Treatments

Factor VIII and factor IX products or bypassing agents (e.g., rFVIIa or aPCC) can be administered for the treatment of breakthrough bleeds in patients receiving HYMPAVZI. Do not use additional doses of HYMPAVZI to treat breakthrough bleeds. Healthcare providers should discuss with all patients and/or caregivers the dose and schedule of the clotting factor concentrates or bypassing agents to use, if required, while receiving HYMPAVZI prophylaxis.

When treating breakthrough bleeds with factor VIII or factor IX products or with bypassing agents, the lowest effective dose according to the product prescribing information is recommended *[see Warnings and Precautions (5.1)]*. Please refer to the Full Prescribing Information for the clotting factor concentrate or bypassing agent being used. For rFVIIa, a maximum dose of 90 mcg/kg body weight per dose and a maximum dosing frequency of every 2 hours is recommended. For aPCC, a maximum dose of 100 units/kg body weight within 24 hours is recommended.

2.6 Temporary Interruption for Surgery and Other Interventions

Management in the Perioperative Setting

HYMPAVZI has not been evaluated in the setting of major surgery. Patients have had minor surgical procedures without discontinuing HYMPAVZI prophylaxis in clinical studies.

For major surgery, pause HYMPAVZI at least 7 days prior and initiate management per local standard of care with clotting factor concentrate or bypassing agent 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 or bypassing agent for dosage guidelines in patients with hemophilia undergoing major surgery. Resumption of HYMPAVZI therapy should consider 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 Dosage and Administration (2.1)]*.

Management in Patients with Acute Severe Illness

There is limited experience with the use of HYMPAVZI in patients with acute severe illness. Reasons to consider temporary dose interruption of HYMPAVZI include occurrence of acute severe illness (e.g., serious infection, sepsis, trauma) in which there may be increased activation of coagulation and which the healthcare provider 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. Resume HYMPAVZI therapy once patient has clinically recovered *[see Dosage and Administration (2.1)]*.

2.7 Pregnancy Testing

Verify that females of reproductive potential are not pregnant prior to initiating HYMPAVZI *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

2.8 Immune Tolerance Induction

The safety and efficacy of HYMPAVZI in patients receiving ongoing Immune Tolerance Induction (ITI), a desensitization strategy for the eradication of inhibitors, have not been established, and no data are available. Careful assessment of the potential benefits and risks should be performed if continuation or initiation of HYMPAVZI during ITI is considered.

3 DOSAGE FORMS AND STRENGTHS

HYMPAVZI (marstacimab-hncq) is a clear and colorless to light yellow solution available as:

Prefilled Syringe

- Injection: 150 mg/mL in a single-dose prefilled syringe
- Injection: 75 mg/0.5 mL in a single-dose prefilled syringe

Prefilled Pen

- Injection: 150 mg/mL in a single-dose prefilled pen
- Injection: 75 mg/0.5 mL in a single-dose prefilled pen

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Events

HYMPAVZI is a tissue factor pathway inhibitor (TFPI) antagonist, and may increase the risk of thromboembolic complications. Venous and arterial thromboembolic events were reported in 0.8% of patients (2/259) treated with HYMPAVZI in the open-label extension study *[see Adverse Reactions (6.1)]*.

Patients with independent risk factors for thromboembolic events may be at increased risk of thromboembolic events with use of HYMPAVZI.

HYMPAVZI has not been studied in patients with a history of previous thromboembolic events *[see Clinical Studies (14.1)]*. Consider the benefit and risk of using HYMPAVZI in patients with known risk factors for thromboembolism.

Interrupt HYMPAVZI prophylaxis if diagnostic findings consistent with thromboembolism occur and manage as clinically indicated.

If factor VIII or factor IX products or bypassing agents are indicated in a patient receiving HYMPAVZI prophylaxis, the minimum effective dose according to the product label is recommended *[see Dosage and Administration (2.5)]*.

5.2 Hypersensitivity
HYMPAVZI may cause hypersensitivity reactions (including but not limited to urticaria and pruritus). If HYMPAVZI-treated patients develop a severe hypersensitivity reaction, advise patients to discontinue HYMPAVZI and seek immediate emergency treatment.

5.3 Embryofetal Toxicity
Based on its mechanism of action, HYMPAVZI may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with HYMPAVZI and for 2 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.4 Increased Laboratory Values of Fibrin D-dimer and Prothrombin Fragment 1.2
Consistent with its mechanism of action and hemostatic effect, HYMPAVZI causes an increase in fibrin D-dimer and prothrombin fragment 1.2 *[see Clinical Pharmacology (12.1, 12.2)]*. Sporadic or transient increases in levels of these biomarkers above physiological values were reported with no associated safety concerns *[see Clinical Pharmacology (12.2)]*. Increased levels of fibrin D-dimer were seen in 10 (8.1%) pediatric patients age 6 to less than 18 years and 6 (4.4%) adults. Increased levels of prothrombin fragment 1.2 were seen in 13 (10.5%) pediatric patients age 6 to less than 18 years and 6 (4.4%) adults. For patients taking HYMPAVZI, these coagulation biomarkers may not be reliable predictive markers for clinical decision-making with suspicion of thrombosis such as deep vein thrombosis (DVT) and pulmonary embolism (PE).

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:
- Thromboembolic Events *[see Warnings and Precautions (5.1)]*
- Hypersensitivity *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of HYMPAVZI was evaluated in adults and pediatric patients 6 years of age and older with severe hemophilia A (FVIII <1%) or moderately severe to severe hemophilia B (FIX ≤2%) with and without inhibitors enrolled in the BASIS and BASIS KIDS studies. A total of 259 patients received the recommended HYMPAVZI prophylaxis loading dose followed by a weekly maintenance dose starting at Day 8 administered subcutaneously *[see Clinical Studies (14.1, 14.2, 14.3)]*. One-hundred-thirty-five (52%) were adults (18 years of age and older), 56 (22%) were adolescents (12 to less than 18 years of age), and 68 (26%) were children (6 to less than 12 years of age). Among patients receiving HYMPAVZI, 90% were exposed for 6 months or longer and 82% were exposed for at least 1 year. The median duration of exposure across the studies was 364 days (min, max: 14, 406 days).

Table 1 summarizes the adverse reactions reported in ≥2% of patients in all age groups who received HYMPAVZI prophylaxis.

Table 1. Adverse Reactions Reported in ≥2% of Patients Treated with HYMPAVZI* By Age Group

Adverse Reaction	Number of Patients 6 to less than 18 Years n (%) (N = 124)	Number of Patients 18 Years and Older n (%) (N = 135)	Number of Patients (All Age Groups) n (%) (N = 259)
Injection site reaction**	19 (15)	11 (8)	30 (12)
Headache***	9 (7)	10 (7)	19 (7)
Pyrexia	12 (10)	3 (2)	15 (6)
Arthralgia	4 (3)	5 (4)	9 (3)
Diarrhea	5 (4)	2 (2)	7 (3)
Pruritus	1 (1)	5 (4)	6 (2)
Rash	2 (2)	3 (2)	5 (2)

* During BASIS and BASIS KIDS studies 12-month active treatment phase

** Injection site reaction is a grouped term which includes the following terms: injection site pruritus, injection site swelling, injection site erythema, injection site bruising, injection site induration, injection site pain, injection site edema, injection site hematoma, injection site hemorrhage, injection site warmth, and injection site urticaria.

*** Headache is a grouped term which includes migraine.

7 DRUG INTERACTIONS

Partial Thromboplastin Time (aPTT) and Prothrombin Time (PT)

No clinically significant differences in standard measures of coagulation including activated partial thromboplastin time (aPTT) and prothrombin time (PT) were observed following marstacimab-hncq therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, HYMPAVZI may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on HYMPAVZI use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Female animal reproduction studies have not been conducted with HYMPAVZI. Although there are no data on marstacimab-hncq, monoclonal antibodies can be actively transported across the placenta, and marstacimab-hncq may cause fetal harm.

The background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of marstacimab-hncq in either human or animal milk, the effects on the breastfed child, or the effects on milk production.

Endogenous maternal IgG and monoclonal antibodies are known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to marstacimab-hncq are unknown.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HYMPAVZI and any potential adverse effects on the breastfed infant from HYMPAVZI or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

HYMPAVZI may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating HYMPAVZI treatment.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with HYMPAVZI and for 2 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of HYMPAVZI to prevent or reduce the frequency of bleeding episodes in hemophilia A or B with and without inhibitors have been established in pediatric patients 6 years of age and older *[see Clinical Studies (14.1, 14.2, 14.3)]*. Use of HYMPAVZI in pediatric patients for this indication is supported by evidence from two open-label, multi-center studies (BASIS and BASIS KIDS). These two studies treated 56 adolescents (12 to less than 18 years of age). BASIS KIDS treated 68 children (6 to less than 12 years of age). Efficacy and adverse reaction profile were comparable between pediatric patients and adults *[see Adverse Reactions (6.1) and Clinical Studies (14.1, 14.2, 14.3)]*. Differences observed in steady-state pharmacokinetic (PK) exposures between pediatric patients and adults were mostly accounted for by body weight *[see Clinical Pharmacology (12.3)]*.

The safety and effectiveness of HYMPAVZI have not been established in pediatric patients younger than 6 years of age.

8.5 Geriatric Use

Two patients 65 years of age and older were enrolled in the clinical studies for hemophilia A or B with or without inhibitors *[see Clinical Studies (14.1, 14.2)]*. Clinical studies of HYMPAVZI did not include sufficient numbers of subjects 65 years of age and over to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for overdose management recommendations.

11 DESCRIPTION

Marstacimab-hncq is a tissue factor pathway inhibitor (TFPI) antagonist, human monoclonal immunoglobulin G Type 1 (IgG1) antibody. Marstacimab-hncq is produced by Chinese hamster ovary (CHO) cells by recombinant DNA technology and has a molecular mass of approximately 146 kDa.

HYMPAVZI (marstacimab-hncq) injection is supplied as a sterile, preservative-free solution for subcutaneous administration. The drug product is supplied as either a single-dose prefilled syringe or as a single-dose prefilled pen. The solution of marstacimab-hncq is clear and colorless to light yellow with a pH of 5.8.

Each 150 mg/mL prefilled syringe or prefilled pen delivers 1 mL of HYMPAVZI. Each 1 mL of HYMPAVZI contains 150 mg of marstacimab-hncq, and the inactive ingredients edetate disodium (0.05 mg), histidine (1.12 mg), L-histidine monohydrochloride (2.67 mg), polysorbate 80 (0.2 mg), and sucrose (85 mg), in Water for Injection, USP.

Each 75 mg/0.5 mL prefilled syringe or prefilled pen delivers 0.5 mL of HYMPAVZI. Each 0.5 mL of HYMPAVZI contains 75 mg of marstacimab-hncq, and the inactive ingredients edetate disodium (0.03 mg), histidine (0.56 mg), L-histidine monohydrochloride (1.34 mg), polysorbate 80 (0.1 mg), and sucrose (43 mg), in Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Marstacimab-hncq is a human monoclonal IgG1 antibody directed against the Kunitz domain 2 (K2) of TFPI to neutralize TFPI activity and enhance coagulation. TFPI is the primary inhibitor of the extrinsic coagulation cascade and negatively regulates thrombin generation within the extrinsic pathway of coagulation by inactivating the protease functions of FXa/FVIIa/TF complex. TFPI binds to and inhibits the factor Xa active site via its second Kunitz inhibitor domain (K2).

12.2 Pharmacodynamics

For adults, adolescents and pediatric patients 6 to less than 12 years of age, marstacimab-hncq causes an increase in total TFPI (comprised of free TFPI and TFPI bound to marstacimab) and downstream biomarkers of thrombin generation such as prothrombin fragment 1+2, peak thrombin, and D-dimer in patients with hemophilia with and without inhibitors. These changes were observed and persisted over a 7-day period following a single subcutaneous dose and were reversible after treatment discontinuation. Sporadic or transient increases in D-dimer and prothrombin fragment 1+2 above physiological values were reported in the study with no associated safety concerns.

There were no clinically relevant differences in pharmacodynamic effects between hemophilia participants with and without inhibitors or between age groups, following weekly subcutaneous administration of marstacimab-hncq.

Drug Interaction

In Vitro Studies

In vitro studies in plasma from patients with hemophilia A and B with inhibitors demonstrated that marstacimab-hncq in combination with rFVIIa resulted in no additive effect on thrombin generation compared to marstacimab-hncq treatment alone. Thrombin generation increased when marstacimab-hncq was used in combination with aPCC compared to marstacimab-hncq treatment alone without exceeding peak thrombin levels achieved in non-hemophilic plasma treated with marstacimab-hncq alone and in some cases were within the range reported for non-hemophilic normal plasma.

12.3 Pharmacokinetics

Estimated mean marstacimab-hncq $C_{min,ss}$, $C_{max,ss}$, and $C_{avg,ss}$ for adults and adolescents weighing at least 25 kg following marstacimab-hncq 150 mg subcutaneous once-weekly administration (with a loading dose of 300 mg subcutaneous), and for pediatric patients 6 to less than 12 years of age weighing at least 19 kg following marstacimab-hncq 75 mg subcutaneous once-weekly administration (with a loading dose of 150 mg subcutaneous) are shown in Table 2.

In adults and adolescents, the marstacimab-hncq area under the plasma concentration-time curve (AUC) and the maximum plasma concentration (C_{max}) increase in a greater than dose-proportional manner over the dose range of 100 mg to 450 mg (0.67 to 3 times the approved recommended dosage).

In adult and adolescent patients, the mean steady-state accumulation ratio for marstacimab-hncq is approximately 4 to 5. Marstacimab-hncq steady-state concentrations are achieved by approximately 60 days (8^{th} or 9^{th} subcutaneous dose) when administered once weekly. Similar results were observed in pediatric patients 6 to less than 12 years of age.

Table 2. Steady-State Marstacimab-hncq Plasma Concentrations Following Once-Weekly Subcutaneous Administration

Parameter	Adults without Inhibitors (150 mg SC QW)	Adults with Inhibitors (150 mg SC QW)	Adolescents without Inhibitors (150 mg SC QW)	Adolescents with Inhibitors (150 mg SC QW)	Pediatric Patients 6 to less than 12 Years without Inhibitors (75 mg SC QW)	Pediatric Patients 6 to less than 12 Years with Inhibitors (75 mg SC QW)
N	99	34	29	21	18	11
$C_{min,ss}$ (mcg/mL)	13.2 (95.5%)	16.1 (77.9%)	30.1 (74.5%)	35.5 (69.0%)	10.6 (67.4%)	16.5 (53.9%)
$C_{max,ss}$ (mcg/mL)	17.7 (79.6%)	21.9 (67.7%)	37.3 (65.9%)	44.7 (63.5%)	21.6 (56.4%)	26.1 (45.4%)
$C_{avg,ss}$ (mcg/mL)	16.1 (84.3%)	19.8 (70.3%)	34.8 (68.7%)	41.4 (65.2%)	17.1 (57.9%)	22.4 (46.8%)

- Data are presented as arithmetic mean (%CV). N = number of participants
- $C_{min,ss}$ = minimum plasma concentration at steady state; $C_{max,ss}$ = maximum plasma concentration at steady state; $C_{avg,ss}$ = average plasma concentration at steady state
- Adults: 18 years and older, Adolescents: 12 to less than 18 years

Absorption

Bioavailability of marstacimab-hncq following subcutaneous administration is approximately 71% for adults, adolescents and pediatric patients 6 to less than 12 years of age. Median T_{max} ranges from 23 to 59 hours following multiple subcutaneous administrations of marstacimab-hncq to patients with hemophilia. No clinically significant differences were seen in marstacimab-hncq bioavailability when administered subcutaneously in the arm, thigh or abdomen.

Distribution

For adults, adolescents and pediatric patients 6 to less than 12 years of age, marstacimab-hncq steady-state apparent volume of distribution is 6.0 L in patients with hemophilia.

Elimination

Marstacimab-hncq is cleared via linear and non-linear mechanisms. Marstacimab-hncq exhibited non-linear pharmacokinetics due to target-mediated drug disposition (TMDD) which occurs when it forms marstacimab-hncq/TFPI complex. Once the target becomes saturated, linear pathway (i.e., catabolism) dominates.

Based on population pharmacokinetic analysis using adult and adolescent data, 90% of marstacimab-hncq is expected to be eliminated by the end of approximately 1 month after the last dose (median time for 50% of drug to be eliminated is approximately 7 to 11 days). Similar results were observed in pediatric patients 6 to less than 12 years of age.

Metabolism
Marstacimab-hncq is expected to be metabolized into small peptides and amino acids by catabolic pathways in the same manner as endogenous IgG.

Specific Populations
No clinically significant differences in pharmacokinetics of marstacimab-hncq were observed in any of the age groups based on race, hemophilia type (A and B), inhibitor status and mild hepatic impairment (total bilirubin >1× to ≤1.5× ULN). In adults and adolescents, no clinically significant differences in pharmacokinetics of marstacimab-hncq were observed based on mild renal impairment (eGFR of 60 to 89 mL/min/1.73 m^2). The effects of geriatric age (>65 years), moderate to severe renal (eGFR <59 mL/min/1.73 m^2) and moderate to severe hepatic (Child Pugh class B and C) impairment on marstacimab-hncq pharmacokinetics are unknown.

Body Weight
Body weight was a significant covariate impacting the pharmacokinetics of marstacimab-hncq. Marstacimab-hncq exposures in adults and adolescents over the body weight range of 25 kg to 120 kg, and exposures in pediatric patients 6 to less than 12 years of age over the body weight range of 19 kg to 59 kg, show a trend for increase in exposure with decrease in body weight. However, dose adjustment based on body weight is not required for any of the age groups.

Pediatric Patients
Patients 12 to less than 18 years of age: Marstacimab-hncq exposures (geometric mean steady-state AUC, C_{max} and C_{min}) were 2.6- to 3.2-fold higher in adolescents compared to adult patients with hemophilia; however, body weight accounts for most of these differences in exposures. These differences in PK did not translate to a clinically relevant difference in levels of the downstream pharmacodynamic marker peak thrombin between adults and adolescents.

Patients 6 to less than 12 years of age: Marstacimab-hncq exposures (geometric mean steady-state AUC, C_{max} and C_{min}) in patients with hemophilia 6 to less than 12 years of age are approximately 1.2- to 1.5-fold higher than those in adult patients with hemophilia and approximately 1.7- to 2.8-fold lower than those in adolescent patients with hemophilia; however, body weight accounts for most of these differences in exposure. Similar to adults and adolescents, these differences in PK do not translate to a clinically relevant difference in levels of the downstream pharmacodynamic markers between the age groups.

12.6 Immunogenicity
The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and the specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies (ADA) in the studies described below with the incidence of ADA in other studies, including those of marstacimab-hncq or of other marstacimab products.

Following weekly subcutaneous marstacimab-hncq dosing in patients with hemophilia 12 years of age and older with and without inhibitors for approximately a year in the BASIS study, 33 of the 167 (19.8%) ADA-evaluable patients treated with marstacimab-hncq developed ADAs. Among the 33 patients who developed ADAs, 8 patients (24.2%) developed neutralizing anti-drug antibodies (NAbs). Subjects who received marstacimab-hncq and developed ADAs had reduced marstacimab-hncq steady-state concentrations, geometric mean decrease was in the range of 19% to 47%, compared to those who did not develop ADAs through the course of the treatment period.

Following weekly subcutaneous marstacimab-hncq dosing in patients with hemophilia 6 to less than 18 years of age with and without inhibitors for approximately a year in the BASIS KIDS study, 14 of the 91 (15.4%) ADA-evaluable patients treated with marstacimab-hncq developed ADAs. Out of the 14 ADA-positive patients, 4 patients were 12 to less than 18 years of age (4/24; 16.7%), 10 patients were 6 to less than 12 years of age

(10/67; 14.9%). Among the 14 patients who developed ADAs, 5 patients (35.7%) developed NAbs, 1 patient was 12 to less than 18 years of age (1/3; 25.0%) and 4 patients were in 6 to less than 12 years of age (4/10; 40.0%). In subjects 12 to less than 18 years of age who received marstacimab-hncq and developed ADAs had reduced marstacimab-hncq steady-state concentrations, geometric mean decrease was in the range of 28% to 64%, compared to those who did not develop ADAs through the course of the treatment period. In subjects 6 to less than 12 years of age who received marstacimab-hncq and developed ADAs had increased marstacimab-hncq steady-state concentrations, geometric mean increase was in the range of 45% to 113%; however, exposure was comparable between ADA-positive and ADA-negative subjects after accounting for body weight.

Although lower mean marstacimab-hncq concentrations were reported in patients aged 12 years and above who were ADA-positive compared to those who were ADA-negative through the course of the treatment period, there was no identified clinically significant effect of ADAs, including NAbs, on safety or efficacy of marstacimab-hncq over the treatment duration of 12 months. Overall, the safety profile of marstacimab-hncq was similar between patients with ADAs (including NAbs) and those without.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to assess marstacimab-hncq for the potential for carcinogenicity or mutagenicity. Marstacimab-hncq did not affect fertility when administered as a repeat dose to male rats at doses up to 1000 mg/kg/dose and an exposure margin of 212-times the exposure at a clinical dose of 300 mg subcutaneous weekly. No effects were observed in male or female reproductive organs in the repeat-dose toxicity studies of up to 6 months in duration in rats and 3 months in duration in cynomolgus monkeys at doses of 1000 mg/kg/dose and 500 mg/kg/dose and exposure margins at least 201- and 219-times, respectively, the AUC exposure at a clinical dose of 300 mg subcutaneous weekly.

14 CLINICAL STUDIES

14.1 Hemophilia A and B without Inhibitors in Adults and Pediatric Patients 12 Years of Age and Older

The efficacy of HYMPAVZI was established in 116 adults and pediatric patients (12 years of age and older and ≥35 kg) with severe hemophilia A (FVIII <1%) without FVIII inhibitors or moderately severe to severe hemophilia B (FIX ≤2%) without FIX inhibitors enrolled in the BASIS study (NCT03938792), open-label, multi-center, two-phase study (observational and treatment phases). Patients with a history of coronary artery disease, venous or arterial thrombosis or ischemic disease were excluded from the study.

Following screening, patients entered a 6-month observation phase and were enrolled to two cohorts based on the factor replacement treatment they were receiving prior to study entry: on-demand or routine prophylaxis. Patients who completed the observation phase were to receive 12 months of HYMPAVZI. Of the 116 patients who received HYMPAVZI, 33 patients were in the on-demand treatment cohort and 83 were in the prophylactic treatment with FVIII or FIX cohort during the observation phase.

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 permitted after 6 months of treatment in patients weighing ≥50 kg and experiencing 2 or more breakthrough bleeds. Fourteen (12%) underwent dose escalation.

The mean annualized bleeding rates (ABRs) for treated bleeds were 39.9 and 7.9 in the observational phase for the on-demand and prophylaxis cohorts, respectively. All patients in the on-demand cohort had one or more target joints at study entry and 36.4% had 3 or more target joints at study entry. In the routine prophylaxis

cohort, 55.4% of the patients had one or more target joints at study entry and 16% had 3 or more target joints at study entry.

The efficacy of HYMPAVZI for each cohort was based upon the ABR of treated bleeds during treatment with HYMPAVZI compared to ABR during the observational phase. Other objectives of the study included evaluation of HYMPAVZI prophylaxis on the incidences of spontaneous bleeds, joint bleeds, target joint bleeds and total bleeds.

Among the 116 patients treated with HYMPAVZI in the BASIS study, the mean age was 32 years (range 13 to 66); 19 patients were 12 to less than 18 years of age and all were male. Fifty-six (56) patients were White, 58 patients were Asian, 1 patient was Black or African American and 1 patient had race information unreported; 12 patients identified as Hispanic or Latino and 104 patients identified as not Hispanic or Latino. The patient population included 91 with hemophilia A and 25 with hemophilia B.

Patients with On-Demand Factor-Based Therapy in Observational Phase

Table 3 shows the efficacy results of HYMPAVZI prophylaxis compared with on-demand factor-based therapy. HYMPAVZI prophylaxis demonstrated superiority over on-demand factor-based therapy in incidences of treated bleeds, spontaneous bleeds, joint bleeds, total bleeds and target joint bleeds.

Table 3. Comparison of Annualized Bleeding Rate with HYMPAVZI Prophylaxis Versus On-Demand Factor-Based Therapy in Patients 12 Years of Age and Older without Factor VIII or Factor IX Inhibitors

Endpoints in the Order of Testing Hierarchy	On-Demand Factor-Based Therapy During 6-Month OP (N = 33)	HYMPAVZI Prophylaxis During 12-Month ATP (N = 33)
Treated Bleeds		
ABR, model-based (95% CI)	39.9 (33.1, 48.1)	3.2 (2.1, 4.9)
Ratio vs. OD (95% CI) p-value	0.08 (0.06, 0.11) <0.0001	
Spontaneous Bleeds, Treated		
ABR, model-based (95% CI)	32.6 (25.8, 41.3)	2.5 (1.6, 3.7)
Ratio vs. OD (95% CI) p-value	0.08 (0.05, 0.11) <0.0001	
Joint Bleeds, Treated		
ABR, model-based (95% CI)	34.5 (27.8, 42.8)	2.9 (1.8, 4.5)
Ratio vs. OD (95% CI) p-value	0.08 (0.06, 0.12) <0.0001	
Total Bleeds, Treated & Untreated		
ABR, model-based (95% CI)	50.0 (42.1, 59.3)	7.4 (5.1, 10.8)
Ratio vs. OD (95% CI) p-value	0.15 (0.11, 0.20) <0.0001	
Target Joint Bleeds, Treated		
ABR, model-based (95% CI)	24.4 (18.3, 32.5)	1.8 (1.1, 3.2)
Ratio vs. OD (95% CI) p-value	0.08 (0.05, 0.12) <0.0001	

- p-value for the null hypothesis that the ratio = 0.5.
- The estimated mean, ratio, and confidence intervals (CIs) for the ABR come from a 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 = Annualized Bleeding Rate; ATP = Active Treatment Phase; CI = Confidence Interval; OD = On-Demand; OP = Observational Phase

Patients with Routine Prophylactic Factor-Based Therapy

Table 4 shows the efficacy results of HYMPAVZI prophylaxis compared with routine prophylactic factor-based therapy. HYMPAVZI prophylaxis demonstrated non-inferiority to routine prophylactic factor-based therapy as measured by ABR of treated bleeds as well as incidences of spontaneous bleeds, joint bleeds, target joint bleeds and total bleeds.

Table 4. Comparison of Annualized Bleeding Rate with HYMPAVZI Prophylaxis Versus Previous Routine Factor-Based Prophylaxis in Patients 12 Years of Age and Older 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		
ABR, model-based (95% CI)	7.9 (5.1, 10.7)	5.1 (3.4, 6.8)
Difference vs. RP (95% CI)	−2.8 (−5.4, −0.2)	
Spontaneous Bleeds, Treated		
ABR, model-based (95% CI)	5.9 (3.6, 8.2)	3.8 (2.3, 5.3)
Difference vs. RP (95% CI)	−2.1 (−4.3, 0.0)	
Joint Bleeds, Treated		
ABR, model-based (95% CI)	5.7 (3.4, 8.0)	4.1 (2.6, 5.7)
Difference vs. RP (95% CI)	−1.6 (−3.7, 0.6)	
Total Bleeds, Treated & Untreated		
ABR, model-based (95% CI)	8.9 (6.0, 11.8)	6.0 (4.1, 7.8)
Difference vs. RP (95% CI)	−2.9 (−5.7, −0.2)	
Target Joint Bleeds, Treated		
ABR, model-based (95% CI)	3.4 (1.6, 5.2)	2.5 (1.3, 3.8)
Difference vs. RP (95% CI)	−0.9 (−2.4, 0.7)	

- 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.
- 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; ATP = Active Treatment Phase; CI = Confidence Interval; OP = Observational Phase; RP = Routine Prophylaxis

14.2 Hemophilia A and B with Inhibitors in Adults and Pediatric Patients 12 Years of Age and Older

The efficacy of HYMPAVZI was established in 48 adults and pediatric patients (12 years of age and older and ≥35 kg) with severe hemophilia A (FVIII <1%) with FVIII inhibitors or moderately severe to severe hemophilia B (FIX ≤2%) with FIX inhibitors enrolled in the BASIS study (NCT03938792), open-label, multi-center, two-phase study (observational and treatment phases). Patients had current or history of high titer inhibitors (≥5 BU/mL) and were in need of treatment with bypassing agents in the last 6 months prior to enrollment. 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.

Following screening, 51 patients entered a 6-month observation phase and received either on-demand (N = 48) or routine prophylactic treatment (N = 3) with bypassing agents (rFVIIa or aPCC). Patients who completed the observation phase were to receive 12 months of HYMPAVZI.

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 permitted after 6 months of treatment in patients weighing ≥50 kg and experiencing 2 or more breakthrough bleeds. Four (7.8%) of 51 patients underwent dose escalation.

The efficacy of HYMPAVZI was based upon the ABR of treated bleeds during treatment with HYMPAVZI compared to ABR during on-demand bypassing agent therapy during the observational phase. Other objectives of the study included evaluation of HYMPAVZI prophylaxis in comparison with on-demand bypassing agent therapy as measured by the incidences of spontaneous bleeds, joint bleeds, target joint bleeds and total bleeds.

Among the 51 male patients treated with HYMPAVZI, the mean age was 27.7 years (range 12 to 75); 25.5% of patients were 12 to less than 18 years, 74.5% were 18 years and older. In this study, 29.4% of patients were White, 54.9% were Asian, 15.7% were Black or African American, 2.0% of patients identified as Hispanic or Latino. All patients had a documented history of inhibitors (78.4% hemophilia A, 21.6% hemophilia B).

Efficacy was established in 48 patients that previously received on-demand bypassing agents before crossing over to HYMPAVZI. This population was characterized by a severe bleeding phenotype. The mean ABR for treated bleeds was 19.8 in the observational phase, prior to crossing over to weekly HYMPAVZI prophylaxis. Of the 48 patients, 70.8% had one or more target joints at study entry and 25.0% had 3 or more target joints at study entry.

Patients with On-Demand Bypassing Agent Therapy in Observational Phase

Table 5 shows the efficacy results of HYMPAVZI prophylaxis compared with on-demand bypassing agent therapy. HYMPAVZI prophylaxis demonstrated superiority over on-demand therapy in incidences of treated bleeds, spontaneous bleeds, joint bleeds, total bleeds and target joint bleeds.

Table 5. Comparison of Annualized Bleeding Rate with HYMPAVZI Prophylaxis Versus On-Demand Bypass Therapy in Patients 12 Years of Age and Older with Factor VIII or Factor IX Inhibitors

Endpoints in the Order of Testing Hierarchy	On-Demand Bypass Therapy During 6-Month OP (N = 48)	HYMPAVZI Prophylaxis During 12-Month ATP (N = 48)
Treated Bleeds		
ABR, model-based (95% CI)	19.8 (16.1, 24.3)	1.4 (0.9, 2.3)
Ratio vs. OD (95% CI)	0.07 (0.04, 0.12)	
p-value	<0.0001	
Spontaneous Bleeds, Treated		
ABR, model-based (95% CI)	15.3 (12.1, 19.3)	0.9 (0.5, 1.4)
Ratio vs. OD (95% CI)	0.06 (0.04, 0.09)	
p-value	<0.0001	
Joint Bleeds, Treated		
ABR, model-based (95% CI)	15.2 (11.9, 19.3)	1.1 (0.6, 2.0)
Ratio vs. OD (95% CI)	0.07 (0.04, 0.14)	
p-value	<0.0001	
Total Bleeds, Treated & Untreated		
ABR, model-based (95% CI)	27.3 (22.5, 33.0)	4.4 (2.7, 7.2)
Ratio vs. OD (95% CI)	0.16 (0.10, 0.25)	
p-value	<0.0001	
Target Joint Bleeds, Treated		
ABR, model-based (95% CI)	6.3 (4.3, 9.2)	0.8 (0.4, 1.7)
Ratio vs. OD (95% CI)	0.13 (0.06, 0.26)	
p-value	0.0001	

- p-value for the null hypothesis that the ratio = 0.5.
- The estimated mean, ratio, and confidence intervals (CIs) for the ABR come from a negative binomial regression model.
- Bleed definitions adapted based on ISTH criteria: Treated bleeds = bleeds treated with bypassing agent; Total bleeds = bleeds treated and not treated with bypassing agent
- ABR = Annualized Bleeding Rate; ATP = Active Treatment Phase; CI = Confidence Interval; OD = On-Demand; OP = Observational Phase

14.3 Hemophilia A and B with or without Inhibitors in Pediatric Patients 6 to less than 18 Years of Age

The efficacy of HYMPAVZI was established in 57 pediatric patients 6 to less than 18 years of age with severe hemophilia A (FVIII <1%) with or without FVIII inhibitors or moderately severe to severe hemophilia B (FIX ≤2%) with or without FIX inhibitors, enrolled in the BASIS KIDS study (NCT05611801), an ongoing open-label, multi-center clinical study. Patients were enrolled sequentially in 2 age groups: 12 to less than 18 years of age (≥25 kg) and 6 to less than 12 years of age (≥19 kg). Patients enrolled in the study required at least 12 months of documented historical bleeding events while on on-demand or on prophylactic treatment with bypassing agents or factor replacement therapy. Patients with a history of coronary artery disease, venous or arterial thrombosis or ischemic disease were excluded from the study. The efficacy of HYMPAVZI was established in these pediatric patients who were dosed at least 12 months before the data cutoff.

Patients 6 to less than 12 years of age (N = 34) received an initial 150 mg loading dose of HYMPAVZI followed by maintenance doses of 75 mg of HYMPAVZI once weekly for 12 months. Patients 12 to less than 18 years of age (N = 23) 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 150 mg of HYMPAVZI once weekly for patients 6 to less than 12 years of age weighing ≥25 kg or 300 mg for patients 12 to less than 18 years of age weighing ≥50 kg was allowed after 3 months for patients experiencing 2 or more breakthrough

bleeds. Two (5.9%) of the 34 patients 6 to less than 12 years of age, and 3 (13%) of the 23 patients 12 to less than 18 years of age underwent dose escalation.

The efficacy of HYMPAVZI was based upon the ABR of treated bleeds during treatment with HYMPAVZI prophylaxis versus ABR of treated bleeds retrospectively collected during the 12-month historical phase. During this historical phase, in the non-inhibitor cohort (N = 36), all patients received routine prophylactic treatment with factor replacement therapy and in the inhibitor cohort (N = 21), patients received either on-demand bypassing agents (N = 14) or routine prophylactic bypassing agents (N = 7). Other endpoints of the study included evaluation of HYMPAVZI prophylaxis as measured by the incidences of spontaneous bleeds, joint bleeds, target joint bleeds and total bleeds.

Among the 57 male patients treated with HYMPAVZI who were evaluated for efficacy, the mean age was 11 years (range 6 to 18); 59.6% of patients were 6 to less than 12 years of age and 40.4% were 12 to less than 18 years of age. In this study 35.1% of patients were White, 49.1% were Asian, 10.5% were Black or African American, 1.8% were American Indian or Alaska Native, and 3.5% race was not reported; 8.8% of patients identified as Hispanic or Latino. The patient population included 35 with hemophilia A (10 with inhibitors; 25 without inhibitors) and 22 with hemophilia B (11 with inhibitors; 11 without inhibitors).

Pediatric Patients 6 to less than 18 Years of Age with Hemophilia A or B without Inhibitors with Historic Routine Prophylactic Factor-Based Therapy
The results for the ABRs of patients without inhibitors with historic routine prophylactic factor-based therapy are shown in Table 6.

Table 6. Annualized Bleeding Rate with HYMPAVZI Prophylaxis in Pediatric Patients by Age Group without Factor VIII or Factor IX Inhibitors with Historic Routine Prophylactic Factor-Based Therapy (interim analysis)

Endpoints	HYMPAVZI Prophylaxis During 12-Month ATP 6 to less than 12 Years (N = 22)	HYMPAVZI Prophylaxis During 12-Month ATP 12 to less than 18 Years (N = 14)	HYMPAVZI Prophylaxis During 12-Month ATP 6 to less than 18 Years (N = 36)
Treated Bleeds			
Mean ABR	1.4	2.6	1.8
99% CI	(0.6, 2.1)	(1.1, 4.1)	(1.1, 2.6)
Median ABR (Q1, Q3)	1.0 (0.0, 2.0)	3.1 (1.0, 4.0)	1.0 (0.5, 3.1)
Spontaneous Bleeds, Treated			
Mean ABR	0.6	1.1	0.8
99% CI	(0.3, 1.4)	(0.4, 3.3)	(0.4, 1.6)
Median ABR (Q1, Q3)	0.0 (0.0, 1.0)	0.5 (0.0, 2.0)	0.0 (0.0, 1.0)
Joint Bleeds, Treated			
Mean ABR	0.6	1.7	1.0
99% CI	(0.2, 0.9)	(0.5, 2.9)	(0.4, 1.6)
Median ABR (Q1, Q3)	0.0 (0.0, 1.0)	1.5 (0.0, 3.1)	0.5 (0.0, 1.6)
Total Bleeds, Treated & Untreated			
Mean ABR	2.3	2.9	2.5
99% CI	(1.5, 3.6)	(1.7, 4.9)	(1.8, 3.6)
Median ABR (Q1, Q3)	2.0 (1.0, 3.0)	3.1 (1.0, 4.1)	2.1 (1.0, 4.0)
Target Joint Bleeds, Treated			
Mean ABR	0.1	0.5	0.2
99% CI	(0.0, 0.6)	(0.1, 2.5)	(0.0, 0.9)
Median ABR (Q1, Q3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)

- The estimated mean and confidence intervals (CIs) for the ABR were based on negative binomial regression model.
- The historical model-based mean ABR of treated bleeds was 3.6 (99% CI: 1.3, 5.8; median: 1.0) for pediatric patients 6 to less than 18 years old.

- ABR = Annualized Bleeding Rate; ATP = Active Treatment Phase (B7841008); CI = Confidence Interval; N = Number of patients who contributed data for analyses; Q1 = 25th percentile; Q3 = 75th percentile

Pediatric Patients 6 to less than 18 Years of Age with Hemophilia A or B with Inhibitors
The results for the ABRs of patients with inhibitors and prior on-demand bypassing therapy are shown in Table 7.

Table 7. Annualized Bleeding Rate with HYMPAVZI Prophylaxis in Pediatric Patients by Age Group with Factor VIII or Factor IX Inhibitors with Historic On-demand Bypassing Agents Therapy (interim analysis)

Endpoints	HYMPAVZI Prophylaxis During 12-Month ATP 6 to less than 12 Years (N = 7)	HYMPAVZI Prophylaxis During 12-Month ATP 12 to less than 18 Years (N = 7)	HYMPAVZI Prophylaxis During 12-Month ATP 6 to less than 18 Years (N = 14)
Treated Bleeds			
Mean ABR	1.3	1.6	1.4
99% CI	(0.5, 3.4)	(0.2, 10.8)	(0.5, 4.5)
Median ABR (Q1, Q3)	1.0 (0.0, 3.0)	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)
Spontaneous Bleeds, Treated			
Mean ABR	0.7	1.4	1.1
99% CI	(0.1, 5.8)	(0.1, 22.3)	(0.2, 6.4)
Median ABR (Q1, Q3)	0.0 (0.0, 2.1)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)
Joint Bleeds, Treated			
Mean ABR	0.9	1.6	1.2
99% CI	(0.3, 2.7)	(0.2, 10.8)	(0.3, 4.6)
Median ABR (Q1, Q3)	1.0 (0.0, 1.0)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)
Total Bleeds, Treated & Untreated			
Mean ABR	1.4	1.7	1.6
99% CI	(0.6, 3.3)	(0.2, 12.3)	(0.6, 4.2)
Median ABR (Q1, Q3)	1.0 (0.0, 3.0)	0.0 (0.0, 2.0)	1.0 (0.0, 2.0)
Target Joint Bleeds, Treated			
Mean ABR	0.6	1.2	0.9
99% CI	(0.1, 4.5)	(0, 93.3)	(0.1, 7.5)
Median ABR (Q1, Q3)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)

- The estimated mean and confidence intervals (CIs) for the ABR were based on negative binomial regression model.
- The historical model-based mean ABR of treated bleeds was 18.9 (99% CI: 14.2, 25.2; median: 15.5) for pediatric patients 6 to less than 18 years old.
- ABR = Annualized Bleeding Rate; ATP = Active Treatment Phase (B7841008); CI = Confidence Interval; N = Number of patients who contributed data for analyses; Q1 = 25th percentile; Q3 = 75th percentile

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

HYMPAVZI (marstacimab-hncq) injection is a sterile, preservative-free, clear and colorless to light yellow solution for subcutaneous administration available as a single-dose prefilled syringe or pen in the following presentations:

Presentation	Package Size	NDC Number
Single-dose prefilled syringe:		
75 mg/0.5 mL	Carton of 1	NDC 0069-1575-01
150 mg/mL	Carton of 1	NDC 0069-1510-01
Single-dose prefilled pen:		
75 mg/0.5 mL	Carton of 1	NDC 0069-0775-01
150 mg/mL	Carton of 1	NDC 0069-2151-01

Prefilled Syringe

Each carton contains a single-dose prefilled syringe (Type I glass) with a plunger stopper (chlorobutyl elastomer) and a stainless steel 27 gauge, ½ inch staked needle with a rigid needle shield (thermoplastic elastomer).

Prefilled Pen

Each carton contains a single-dose prefilled pen with needle guard. 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 rigid needle shield (thermoplastic elastomer).

HYMPAVZI is not made with natural rubber latex.

16.2 Recommended Storage and Handling

- Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light.
- If needed, HYMPAVZI may be stored one time at room temperature [up to 86°F (30°C)] in its original carton to protect from light for up to 7 days. Once stored at room temperature, do not return to the refrigerator and discard after 7 days.
- Do not freeze.
- Do not shake.

17 PATIENT COUNSELING INFORMATION

- Advise the patient and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Ensure that patients and caregivers who will administer HYMPAVZI receive appropriate training and instruction on the proper storage, use and handling of HYMPAVZI from a healthcare professional.

Thromboembolic Events

Inform patients and/or caregivers that HYMPAVZI increases coagulation potential. Discuss the appropriate dosing of concomitant agents such as FVIII or FIX with the patient prior to starting on HYMPAVZI prophylaxis. Advise the patient to discontinue HYMPAVZI and seek immediate medical attention if any signs or symptoms of thromboembolism occur *[see Warnings and Precautions (5.1)]*.

Hypersensitivity

Inform patients and/or caregivers that hypersensitivity reactions such as rash and pruritus are possible. Advise patients to discontinue HYMPAVZI and seek immediate emergency treatment if a severe hypersensitivity reaction occurs *[see Warnings and Precautions (5.2)]*.

Pregnancy

Advise female patients of reproductive potential to use effective contraception during treatment with HYMPAVZI and for 2 months after the last dose. Advise patients to report known pregnancies *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.



Manufactured by
Pfizer Inc.
New York, NY 10001
US License No. 2001

Distributed by
Pfizer Labs
Division of Pfizer Inc.
New York, NY 10001

LAB-1556-4.0

PATIENT INFORMATION
HYMPAVZI® (him-PAV-zee)
(marstacimab-hncq)
injection, for subcutaneous use

Important information:

- **Before you start using HYMPAVZI**, **it is very important to talk to your healthcare provider about using factor VIII and factor IX products or bypassing agents** (products that help blood clot but work in a different way than HYMPAVZI).
- Your healthcare provider may prescribe factor VIII, factor IX medicines, or bypassing agents to treat episodes of breakthrough bleeding during your treatment with HYMPAVZI. Carefully follow your healthcare provider's instructions regarding when to use these medicines and the prescribed dose during your treatment with HYMPAVZI. **Do not use additional doses of HYMPAVZI to treat breakthrough bleeds**.

What is HYMPAVZI?

HYMPAVZI is a prescription medicine used regularly to prevent or reduce the frequency of bleeding episodes in adults and children 6 years of age and older with:

- hemophilia A with or without factor VIII inhibitors, **or**
- hemophilia B with or without factor IX inhibitors.

It is not known if HYMPAVZI is safe and effective in people receiving ongoing Immune Tolerance Induction (ITI).

It is not known if HYMPAVZI is safe and effective in children younger than 6 years of age.

Before using HYMPAVZI, tell your healthcare provider about all of your medical conditions, including if you:

- have a planned surgery. Your healthcare provider may stop treatment with HYMPAVZI before your surgery. Talk to your healthcare provider about when to stop using HYMPAVZI and when to start it again if you have a planned surgery.
- have a severe short-term (acute) illness such as an infection or injury.
- have been told that you have a risk for blood clots.
- are pregnant or plan to become pregnant. HYMPAVZI may harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider will do a pregnancy test before you start your treatment with HYMPAVZI.
  - Use effective birth control (contraception) during treatment with HYMPAVZI and for 2 months after the last dose of HYMPAVZI.
  - Tell your healthcare provider right away if you become pregnant or think that you may be pregnant during treatment with HYMPAVZI.
- are breastfeeding or plan to breastfeed. It is not known if HYMPAVZI passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use HYMPAVZI?

See the detailed "Instructions for Use" that comes with your HYMPAVZI for information on how to inject a dose of HYMPAVZI, and how to properly throw away (dispose of) used HYMPAVZI prefilled syringe or HYMPAVZI prefilled pen.

- Use HYMPAVZI exactly as prescribed by your healthcare provider.
- Your healthcare provider will provide instructions for stopping (discontinuing) your current treatment when switching from factor- or non-factor-based medicines or bypassing agents to HYMPAVZI.
- HYMPAVZI comes in two different strengths in a single-dose prefilled syringe or single-dose prefilled pen.
- HYMPAVZI is given as an injection under your skin (subcutaneous injection) by you or your caregiver.
- People 12 years of age and older, or their caregiver may inject HYMPAVZI if your healthcare provider decides that it is appropriate. Your healthcare provider should show you or your caregiver how to inject HYMPAVZI before the first injection.
- Do not inject yourself or someone else until you have been shown how to inject HYMPAVZI.
- Inject HYMPAVZI 1 time a week on the same day each week. Inject HYMPAVZI at any time of day.
- **Dosing for adults and children 12 years of age and older:**
  - Your first dose (loading dose) of HYMPAVZI is 300 mg (two 150 mg injections). Then you will inject a weekly (maintenance) dose as prescribed by your healthcare provider.
  - If you miss a maintenance dose of 150 mg of HYMPAVZI:
    - Give the dose as soon as possible before the day of your next scheduled dose, and then continue with your usual weekly dosing schedule. You may inject your next dose at your regularly scheduled time or continue

dosing based on the new day you injected your missed dose. In case you are not sure when to inject HYMPAVZI, call your healthcare provider.
    - If more than 13 days have passed since your last dose was given, you will need to restart with a loading dose. Call your healthcare provider right away for dosing instructions.
  - If you miss 1 or more doses of maintenance dose of 300 mg of HYMPAVZI:
    - Give a dose as soon as possible, and then continue with your usual weekly dosing schedule. You may inject your next dose at your regularly scheduled time or continue dosing based on the new day you injected your missed dose. In case you are not sure when to inject HYMPAVZI, call your healthcare provider.
- **Dosing for children 6 years to less than 12 years of age:**
  - Your first dose (loading dose) of HYMPAVZI is 150 mg (one 150 mg injection or two 75 mg injections) as prescribed by your healthcare provider. Then you will inject a weekly (maintenance) dose as prescribed by your healthcare provider.
  - If you miss a maintenance dose of 75 mg of HYMPAVZI:
    - Give the dose as soon as possible before the day of your next scheduled dose, and then continue with your usual weekly dosing schedule. You may inject your next dose at your regularly scheduled time or continue dosing based on the new day you injected your missed dose. In case you are not sure when to inject HYMPAVZI, call your healthcare provider.
    - If more than 13 days have passed since your last dose was given, you will need to restart with a loading dose. Call your healthcare provider right away for dosing instructions.
  - If you miss 1 or more doses of maintenance dose of 150 mg of HYMPAVZI:
    - Give a dose as soon as possible, and then continue with your usual weekly dosing schedule. You may inject your next dose at your regularly scheduled time or continue dosing based on the new day you injected your missed dose. In case you are not sure when to inject HYMPAVZI, call your healthcare provider.
- If you inject too much HYMPAVZI, call your healthcare provider or the Poison Help Line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of HYMPAVZI?

HYMPAVZI may cause serious side effects, including:

- **blood clots (thromboembolic events).** HYMPAVZI may increase the risk for your blood to clot in blood vessels in your arm, leg, lung, or head and can be life-threatening. Blood clots have happened in people using HYMPAVZI. You may have an increased risk of blood clots if you have certain risk factors. Stop using HYMPAVZI and get medical help right away if you develop any of these signs or symptoms of blood clots:
  - swelling or pain in arms or legs
  - redness or discoloration in your arms or legs
  - shortness of breath
  - pain in chest or upper back
  - fast heart rate
  - cough up blood
  - feel faint
  - headache
  - numbness in your face
  - eye pain or swelling
  - trouble seeing
- **allergic reactions.** HYMPAVZI may cause allergic reactions, including rash and itching. Stop using HYMPAVZI and get medical help right away if you develop any of the following symptoms of a severe allergic reaction:
  - swelling of your face, lips, mouth, or tongue
  - trouble breathing
  - wheezing
  - dizziness or fainting
  - fast heartbeat or pounding in your chest
  - sweating

The most common side effects of HYMPAVZI include:

- swelling, hardening, redness, bruising, bleeding, and pain at injection site
- headache
- fever
- joint pain
- diarrhea
- itching
- rash

These are not all of the possible side effects of HYMPAVZI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store HYMPAVZI?

- Store HYMPAVZI in a refrigerator at 36°F to 46°F (2°C to 8°C).
- Store HYMPAVZI in the original carton to protect from light.
- If needed, HYMPAVZI may be stored one time at room temperature up to 86°F (30°C) in its original carton for up to 7 days. **Do not** return HYMPAVZI to the refrigerator after storing at room temperature.
- Throw away (dispose of) HYMPAVZI that has been left out of the refrigerator for more than 7 days.
- Do not freeze HYMPAVZI.
- Do not shake HYMPAVZI.

Keep HYMPAVZI and all medicines out of the reach of children.

General information about the safe and effective use of HYMPAVZI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use HYMPAVZI for a condition for which it was not prescribed. Do not give HYMPAVZI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about HYMPAVZI that is written for health professionals.

What are the ingredients in HYMPAVZI?

Active ingredient: marstacimab-hncq

Inactive ingredients: edetate disodium, histidine, L-histidine monohydrochloride, polysorbate 80, sucrose, and water for injection

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

Manufactured by
Pfizer Inc.
New York, NY 10001

US License No. 2001
Distributed by: Pfizer Labs, Division of Pfizer Inc., New York, NY 10001
LAB-1575-3.0

For more information, go to website www.HYMPAVZI.com or call 1-800-438-1985.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 6/2026

INSTRUCTIONS FOR USE
HYMPAVZI® (him-PAV-zee)
(marstacimab-hncq)
injection, for subcutaneous use
150 mg single-dose prefilled syringe

This Instructions for Use contains information on how to inject HYMPAVZI.

Read this Instructions for Use carefully before using HYMPAVZI Prefilled Syringe and each time you get a refill prescription as there may be new information.

People 12 years of age and older, or their caregiver, may inject HYMPAVZI if your healthcare provider decides it is appropriate. Your healthcare provider should show you or your caregiver how to prepare and inject HYMPAVZI before you use it for the first time. **Do not inject yourself or someone else until you have been shown how to inject HYMPAVZI.**

Important Information You Need to Know Before Injecting HYMPAVZI

- Each HYMPAVZI Prefilled Syringe is a Single-Dose Prefilled Syringe (called “Syringe” in this Instructions for Use). The HYMPAVZI Prefilled Syringe contains 150 mg of HYMPAVZI for injection under the skin (subcutaneously).
- **Do not** inject HYMPAVZI into a vein.
- To help you remember when to inject HYMPAVZI, you can mark your calendar ahead of time. Call your healthcare provider if you or your caregiver have any questions about the right way to inject HYMPAVZI, or call the helpline at 1-888-496-7289 (1-888 HYMPAV-Z).
- Use HYMPAVZI exactly as prescribed by your healthcare provider.
- HYMPAVZI is not made with natural rubber latex.

Storing HYMPAVZI

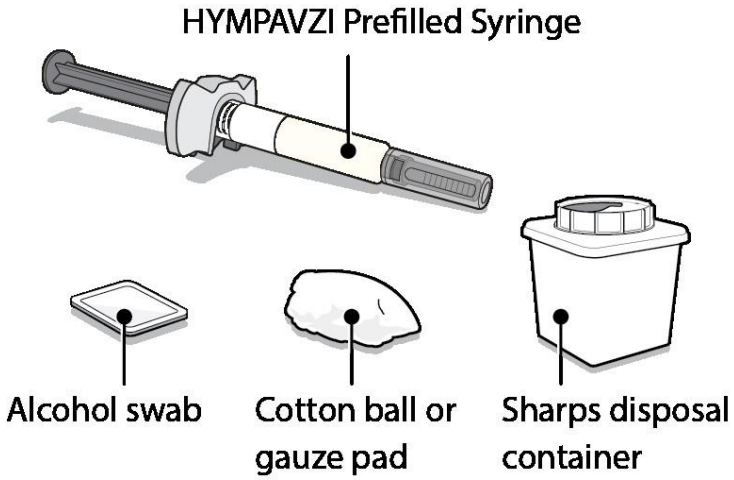
- Store HYMPAVZI in a refrigerator at 36°F to 46°F (2°C to 8°C).
- Store HYMPAVZI in the original carton to protect from light.
- If needed, HYMPAVZI may be stored one time at room temperature, up to 86°F (30°C) in the original carton for up to 7 days. **Do not** return HYMPAVZI to the refrigerator after storing at room temperature.
- Throw away (dispose of) HYMPAVZI that has been left out of the refrigerator for more than 7 days.
- **Do not** freeze HYMPAVZI.
- **Do not** shake HYMPAVZI.
- **Do not** use past the expiration date (Exp) printed on the HYMPAVZI Prefilled Syringe.
- **Keep HYMPAVZI and all medicines out of the reach of children.**

Supplies Needed For HYMPAVZI Injection

Gather the following supplies on a clean flat surface:

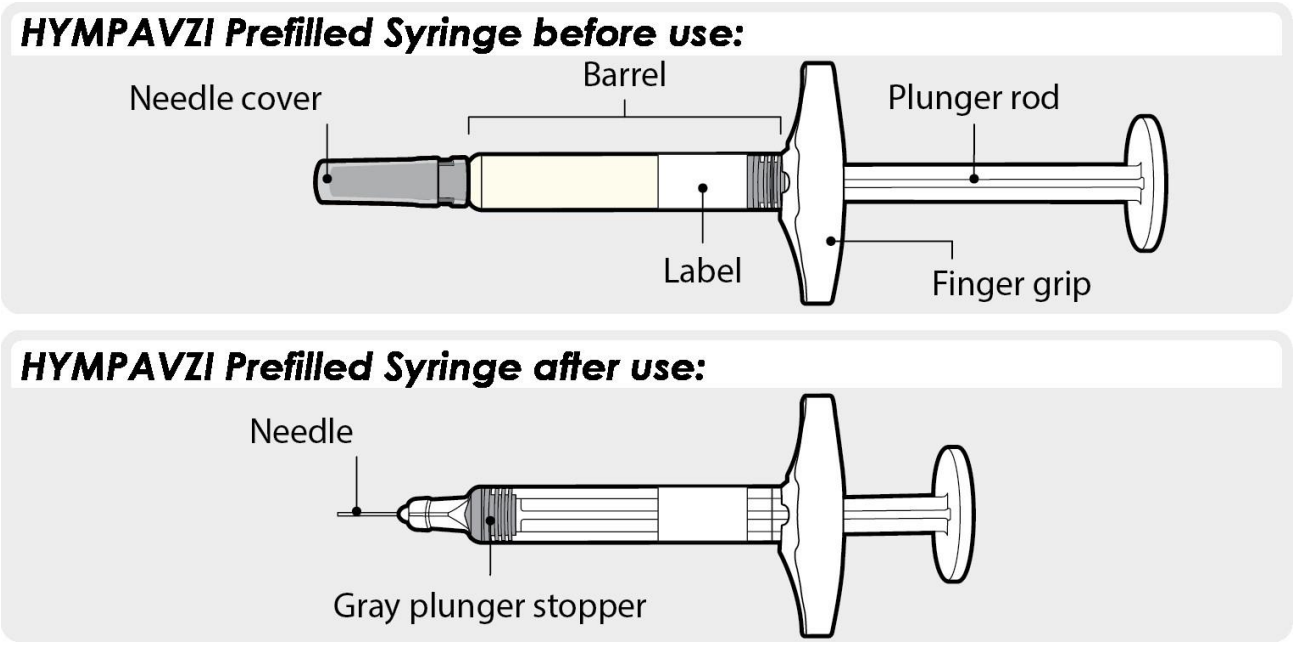
Included in the carton:
- 1 HYMPAVZI Prefilled Syringe

Not included in the carton:
- 1 alcohol swab
- 1 cotton ball or gauze pad
- 1 FDA-cleared sharps disposal container for Syringe disposal (see "**Step 11 – Disposal of Syringe**" and "**Safe Syringe Disposal**" information section)



HYMPAVZI Prefilled Syringe

Always hold HYMPAVZI Prefilled Syringe by the barrel to prevent damage.



Preparing to Inject HYMPAVZI

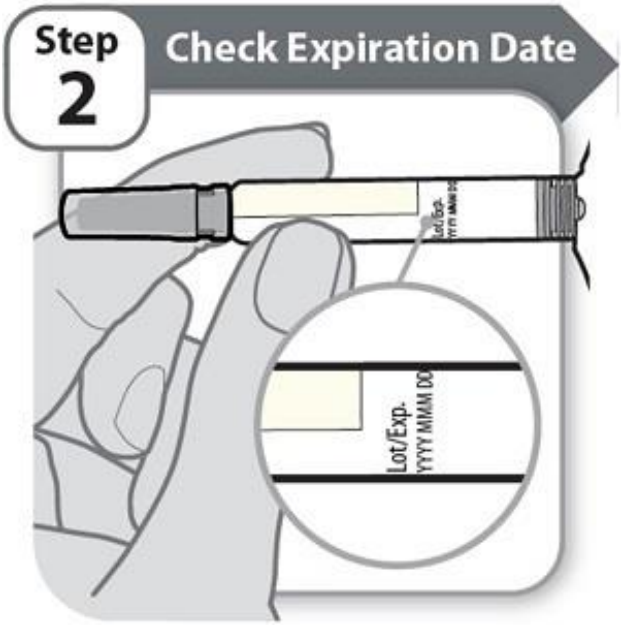
Step 1 – Getting Ready

- **Remove** the Syringe from its carton and keep out of direct sunlight.
- **Make sure** the name HYMPAVZI appears on the carton and Syringe label.
- **Check the Syringe** for any visible damage such as cracks or leaks.
- **Wash and dry** your hands.
- **Do not remove the needle cover until you are ready to inject.**
- **Throw away (dispose of)** the Syringe if it is damaged, or if the Syringe or the carton containing the Syringe has been dropped.
- **Do not** use the Syringe if:
  - it has been stored in direct light. Exposure to room light during dose preparation and injection is acceptable.
  - it has been frozen or thawed, or it has been out of the refrigerator for more than 7 days.

Note: For a more comfortable injection, allow the Syringe to warm at room temperature up to 86°F (30°C) in the carton away from direct sunlight for about 15 to 30 minutes.

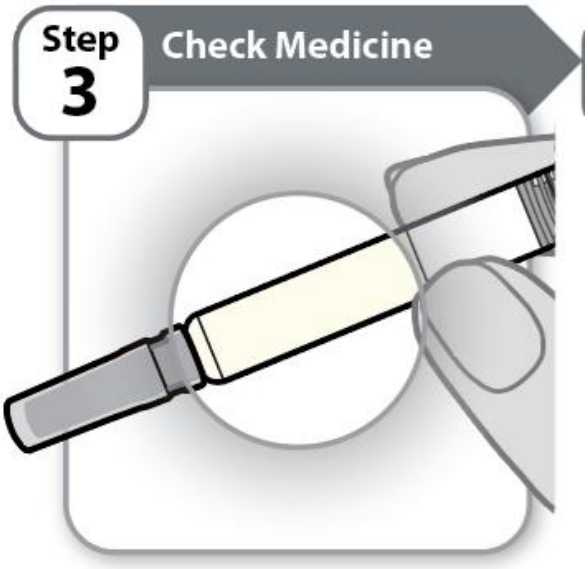
Do not use any other methods to warm up the Syringe, such as warming the Syringe in a microwave or hot water.

Step 2 – Check Expiration Date



- **Check** the expiration date (Exp) printed on the Syringe label.
- **Do not** use if the expiration date (Exp) has passed.

Step 3 – Check Medicine

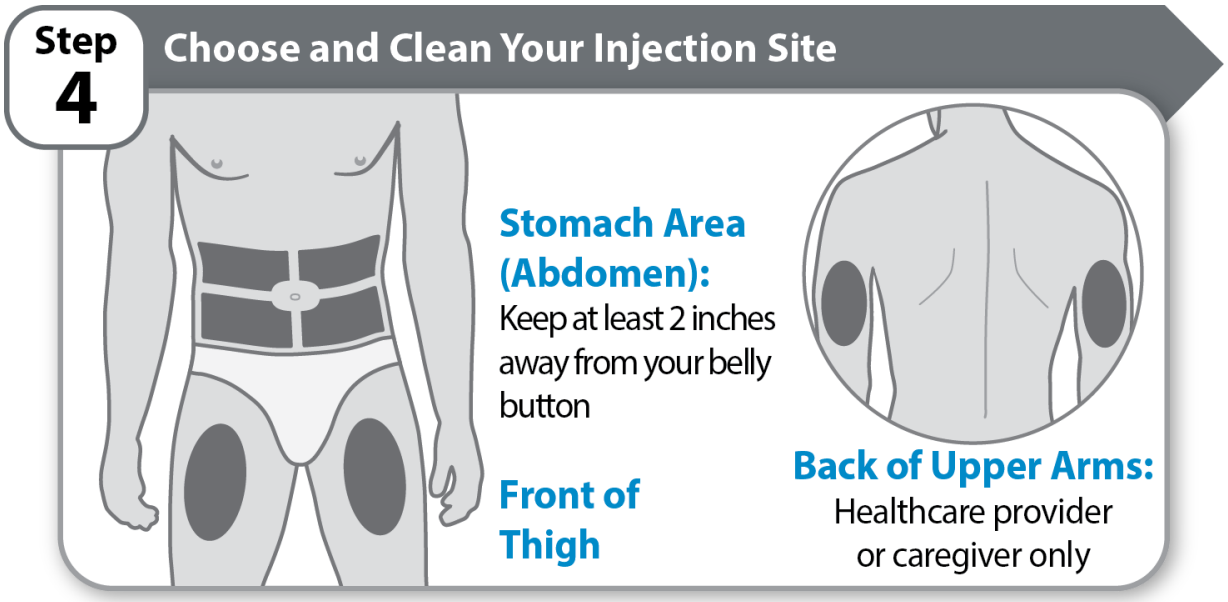


- **Gently** tilt the Syringe back and forth.
- **Look** carefully at the medicine in the Syringe.
  - The medicine should be clear and colorless to light yellow.
  - **Do not** use the Syringe if the medicine is cloudy, dark yellow, or contains flakes or particles.

Note: It is normal to see air bubbles in the Syringe.

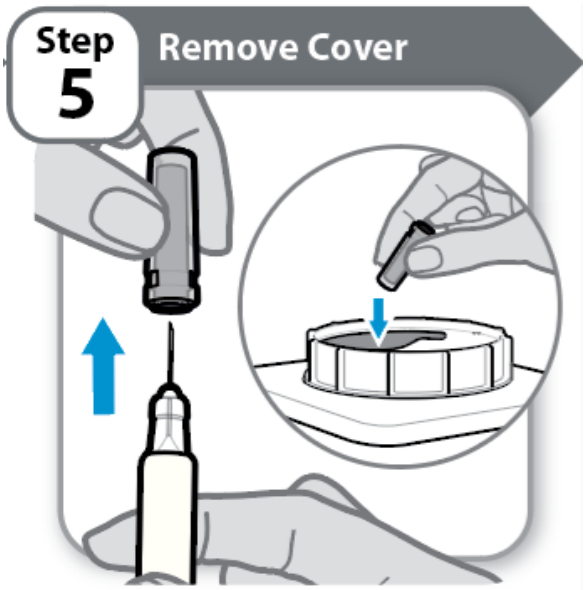
If you have any questions about the medicine, contact your healthcare provider.

Step 4 – Choose and Clean Your Injection Site



- **Choose** an injection site on your stomach area (abdomen) or front of thigh unless a different site has been suggested by your healthcare provider. HYMPAVZI may also be injected into the back of your upper arms by a healthcare provider or caregiver only. Keep at least 2 inches away from your belly button.
- **Change (rotate)** the injection site each time you give yourself an injection of HYMPAVZI and away from any other medicine given under your skin. You may use the same area of your body but be sure to choose a different injection site in that area.
- **Clean** the injection site with soap and water, or an alcohol swab.
- **Allow** the site to air dry. **Do not** touch, fan, or blow on the cleaned injection site.
- **Do not** inject HYMPAVZI into bony areas or areas on your skin that are bruised, red, sore (tender) or hard. Avoid injecting into areas with scars or stretch marks.
- **Do not** inject HYMPAVZI into a vein.
- **Do not** inject HYMPAVZI through your clothes.

Step 5 – Remove Cover



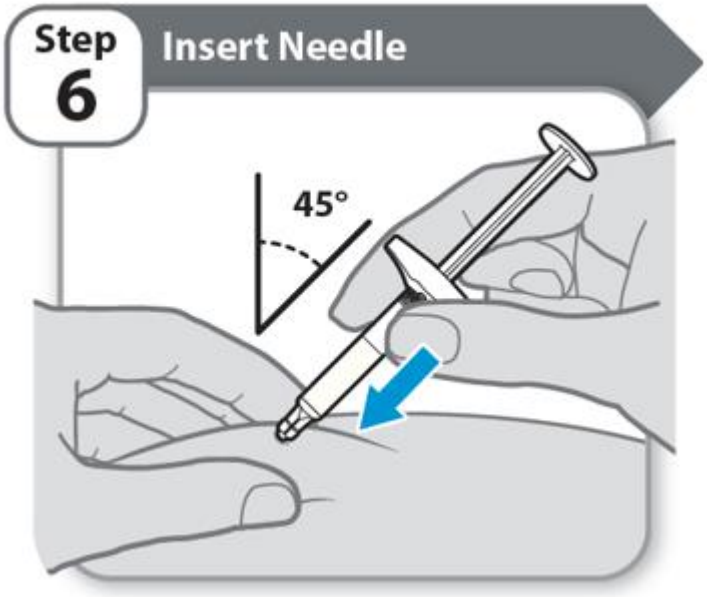
- **Hold** the Syringe by the barrel.
- **Pull** the needle cover straight off carefully.
- **Put** the needle cover into an FDA-cleared sharps disposal container right away. You will not need it again.
- **Do not** touch the needle or let it touch any surfaces.

Note: It is normal to see a few drops of medicine at the needle tip.

Caution: Handle the Syringe with care to avoid an accidental needle injury.

Injecting HYMPAVZI

Step 6 – Insert Needle

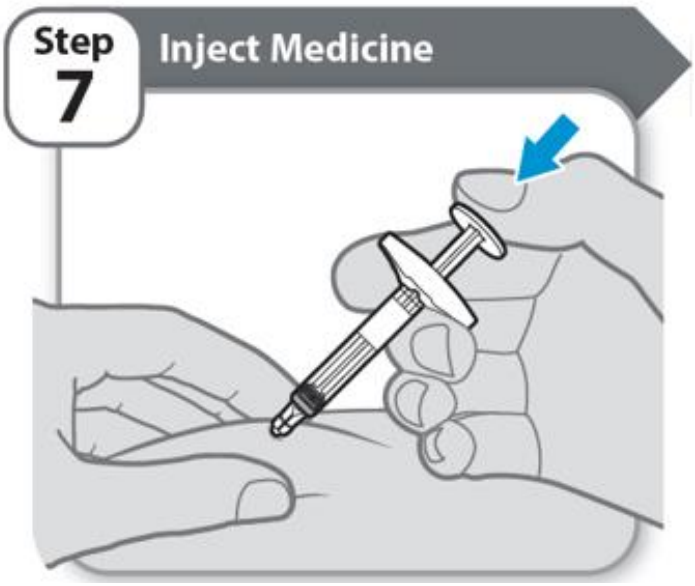


- **Pinch** your cleaned skin between your thumb and fingers to create a firm surface.
- **Fully insert** the needle into your skin at a 45° angle, as shown. **Do not** hold or push on the plunger while inserting the needle.

Keep your skin pinched throughout the injection.

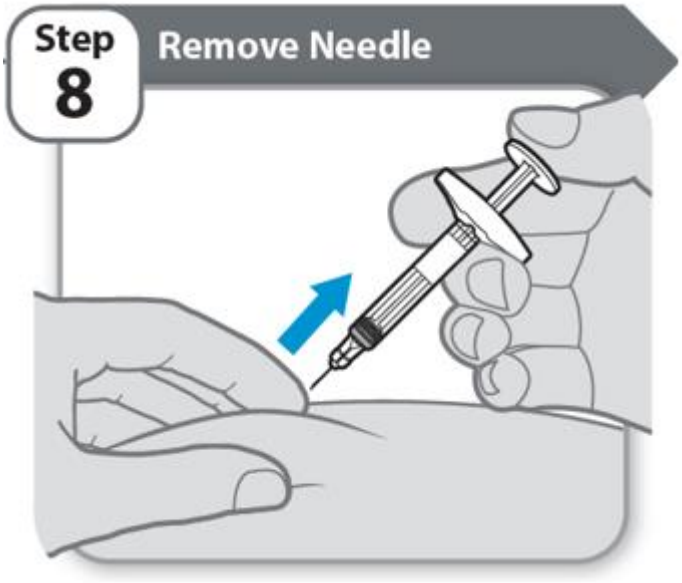
Caution: If you change your mind where to inject after inserting the needle into your skin, you will need to throw away (dispose of) the Syringe and get a new HYMPAVZI Prefilled Syringe.

Step 7 – Inject Medicine



- **Slowly inject** all of HYMPAVZI by gently pushing the plunger rod all the way down, until the barrel is empty.

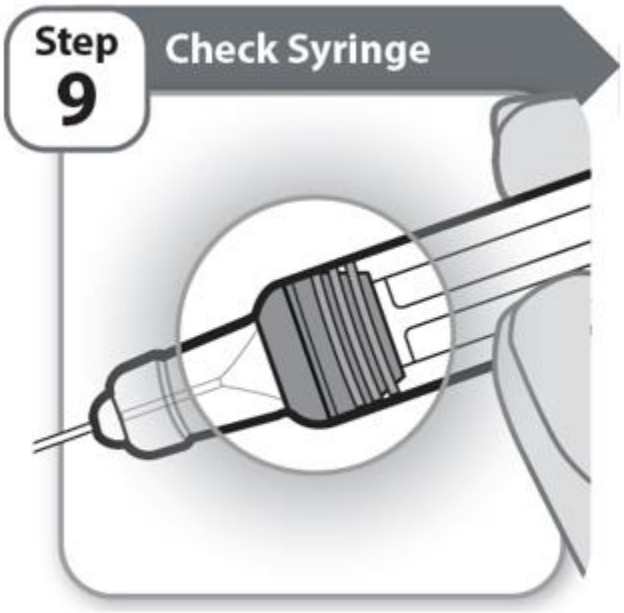
Step 8 – Remove Needle



- **Pull** the needle and Syringe out of your skin at the same angle as inserted.

Note: If you see a small drop of medicine on your skin, wait a little longer before removing the needle when you give your next injection.

Step 9 – Check Syringe



- **Check** the Syringe to make sure the gray plunger stopper is in the position shown.

If the gray plunger stopper is not in the position shown, this means you have not received a full dose. Call your healthcare provider for help.

Never re-insert the needle.

Do not inject another dose.

Step 10 – After Care



- **Press** lightly on the injection site for a few seconds with a clean cotton ball or gauze pad if you see a drop of blood.
- **Do not** rub the area.

Note: If bleeding does not stop, contact your healthcare provider.

Note: If your prescribed dose requires 2 injections of HYMPAVZI, repeat steps 1-10. Change (rotate) the injection site each time you give yourself an injection of HYMPAVZI. You may use the same area of your body but be sure to choose a different injection site in that area.

Step 11 – Disposal of Syringe



- **Put** the used Syringe in an FDA-cleared sharps disposal container right away after use.

Never re-cap the needle.

- **Do not** throw away (dispose of) Syringes in the household trash.

Note: If you do not have an FDA-cleared sharps disposal container, please see the "**Safe Syringe Disposal**" information section.

Safe Syringe Disposal

- **Always throw away** (dispose of) Syringes in a sharps disposal container. **Do not** dispose of Syringes in the household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that:
  - is made of heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - is upright and stable during use,
  - is leak-resistant, and
  - is properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to throw away (dispose of) your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about safe sharps disposal for the state you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** recycle your used sharps disposal container.



Manufactured by
Pfizer Inc.
New York, NY 10001
US License No. 2001

Distributed by
Pfizer Labs
Division of Pfizer Inc.
New York, NY 10001

LAB-1576-3.0

For more information, go to www.pfizer.com or call 1-800-438-1985.

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: 6/2026

INSTRUCTIONS FOR USE
HYMPAVZI® (him-PAV-zee)
(marstacimab-hncq)
injection, for subcutaneous use
150 mg single-dose prefilled pen

This Instructions for Use contains information on how to inject HYMPAVZI.

Read this Instructions for Use carefully before using HYMPAVZI Prefilled Pen and each time you get a refill prescription as there may be new information.

People 12 years of age and older, or their caregiver, may inject HYMPAVZI if your healthcare provider decides it is appropriate. Your healthcare provider should show you or your caregiver how to prepare and inject HYMPAVZI before you use it for the first time. **Do not inject yourself or someone else until you have been shown how to inject HYMPAVZI.**

Important Information You Need to Know Before Injecting HYMPAVZI

- Each HYMPAVZI Prefilled Pen is a Single-Dose Prefilled Pen (called “Pen” in this Instructions for Use). The HYMPAVZI Prefilled Pen contains 150 mg of HYMPAVZI for injection under the skin (subcutaneously).
- **Do not** inject HYMPAVZI into a vein.
- To help you remember when to inject HYMPAVZI, you can mark your calendar ahead of time. Call your healthcare provider if you or your caregiver have any questions about the right way to inject HYMPAVZI, or call the helpline at 1-888-496-7289 (1-888 HYMPAV-Z).
- Use HYMPAVZI exactly as prescribed by your healthcare provider.
- HYMPAVZI is not made with natural rubber latex.

Storing HYMPAVZI

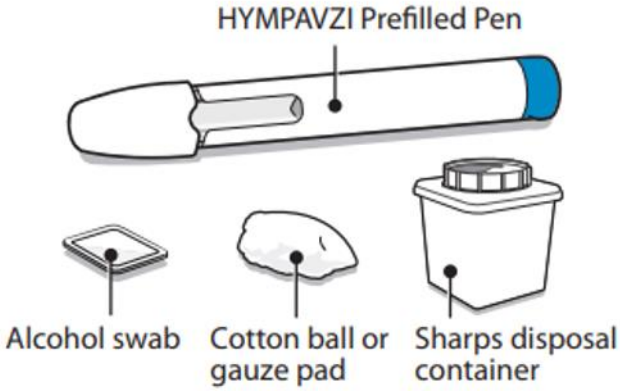
- Store HYMPAVZI in a refrigerator at 36°F to 46°F (2°C to 8°C).
- Store HYMPAVZI in the original carton to protect from light.
- If needed, HYMPAVZI may be stored one time at room temperature, up to 86°F (30°C) in the original carton for up to 7 days. **Do not** return HYMPAVZI to the refrigerator after storing at room temperature.
- Throw away (dispose of) HYMPAVZI that has been left out of the refrigerator for more than 7 days.
- **Do not** freeze HYMPAVZI.
- **Do not** shake HYMPAVZI.
- **Do not** use past the expiration date (EXP) printed on the HYMPAVZI Prefilled Pen.
- **Keep HYMPAVZI and all medicines out of the reach of children.**

Supplies Needed For HYMPAVZI Injection

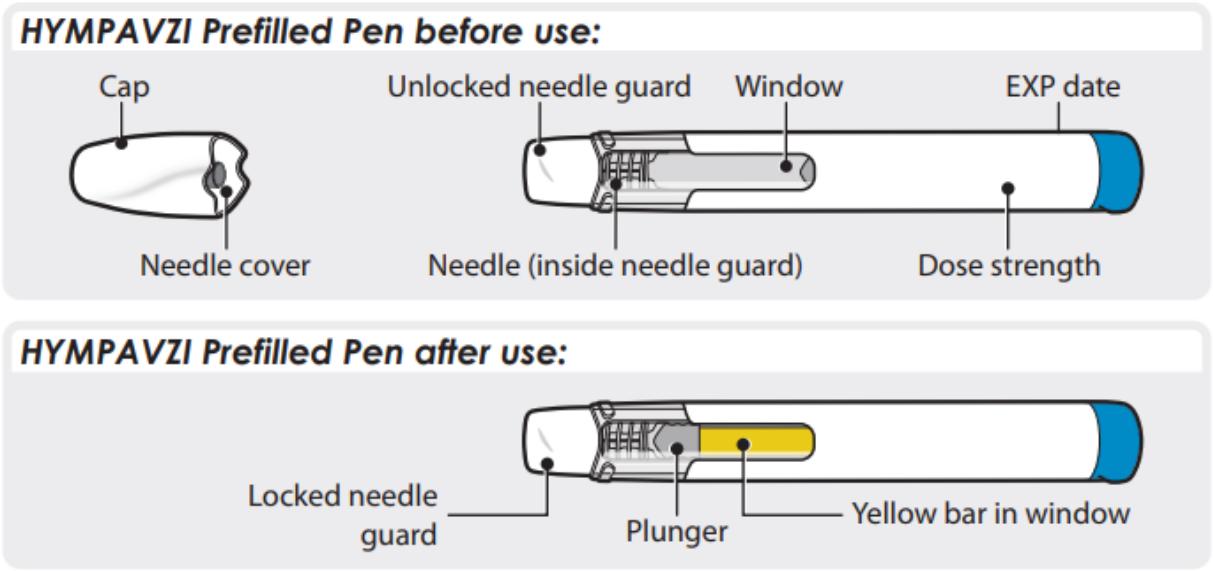
Gather the following supplies on a clean flat surface:

Included in the carton:
- 1 HYMPAVZI Prefilled Pen

Not included in the carton:
- 1 alcohol swab
- 1 cotton ball or gauze pad
- 1 FDA-cleared sharps disposal container for Pen disposal (see "**Step 10 – Disposal of Pen**" and "**Safe Pen Disposal**" information section)



HYMPAVZI Prefilled Pen



Preparing to Inject HYMPAVZI

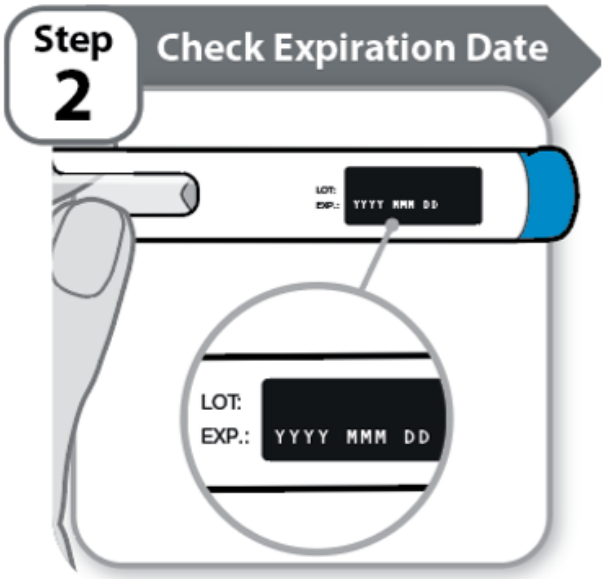
Step 1 – Getting Ready

- **Remove** the Pen from its carton and keep out of direct sunlight.
- **Make sure** the name HYMPAVZI appears on the carton and Pen label.
- **Check the Pen** for any visible damage such as cracks or leaks.
- **Wash and dry** your hands.
- **Do not remove the cap until you are ready to inject.**
- **Throw away (dispose of)** the Pen if it is damaged, or if the Pen or the carton containing the Pen has been dropped.
- **Do not** use the Pen if:
  - it has been stored in direct light. Exposure to room light during dose preparation and injection is acceptable.
  - it has been frozen or thawed, or it has been out of the refrigerator for more than 7 days.

Note: For a more comfortable injection, allow the Pen to warm at room temperature up to 86°F (30°C) in the carton away from direct sunlight for about 15 to 30 minutes.

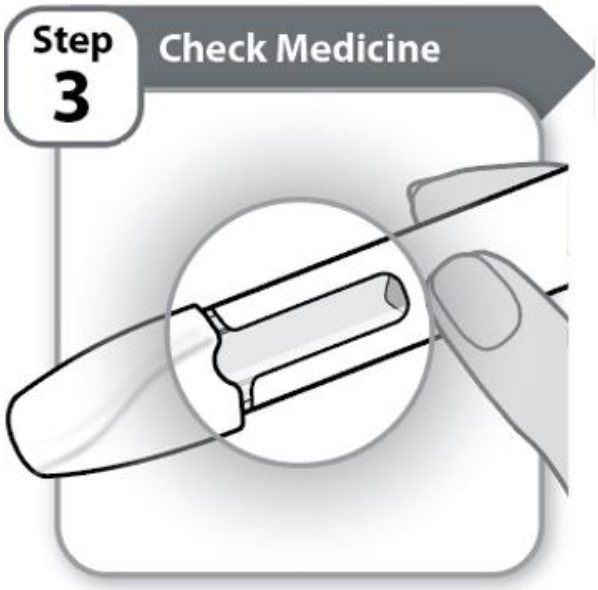
Do not use any other methods to warm up the Pen, such as warming the Pen in a microwave or hot water.

Step 2 – Check Expiration Date



- **Check** the expiration date (EXP) printed on the Pen label.
- **Do not** use if the expiration date (EXP) has passed.

Step 3 – Check Medicine

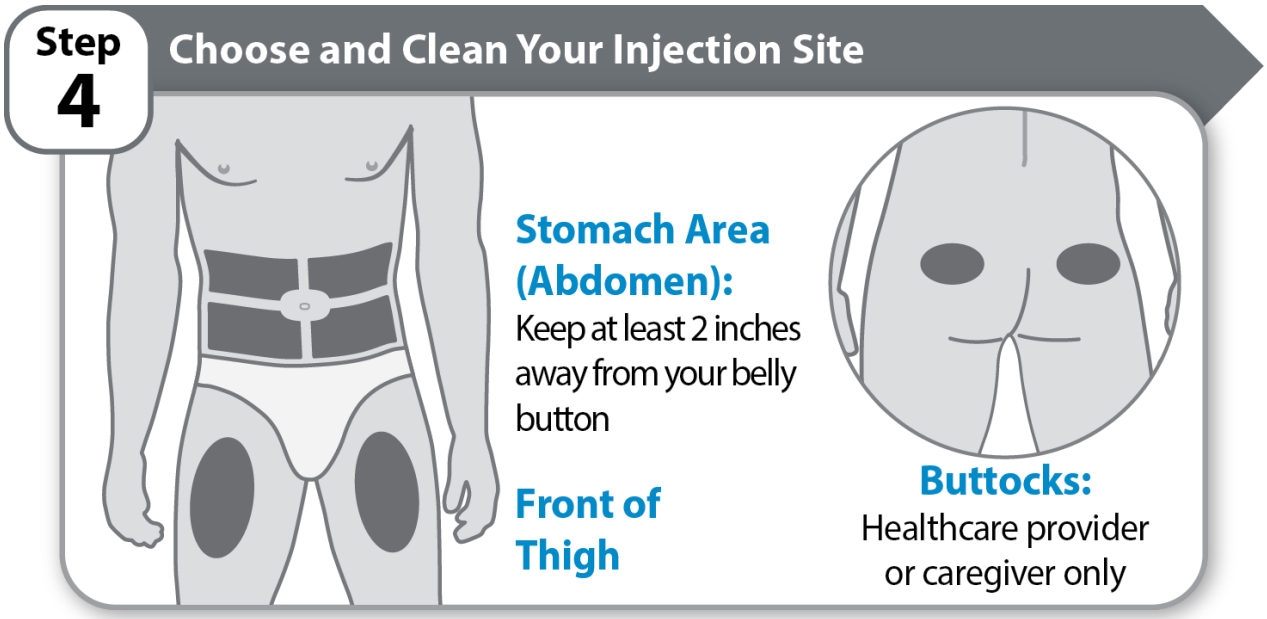


- **Look** carefully at the medicine through the window on the Pen.
  - The medicine should be clear and colorless to light yellow.
  - **Do not** use the Pen if the medicine is cloudy, dark yellow, or contains flakes or particles.

Note: It is normal to see air bubbles in the window.

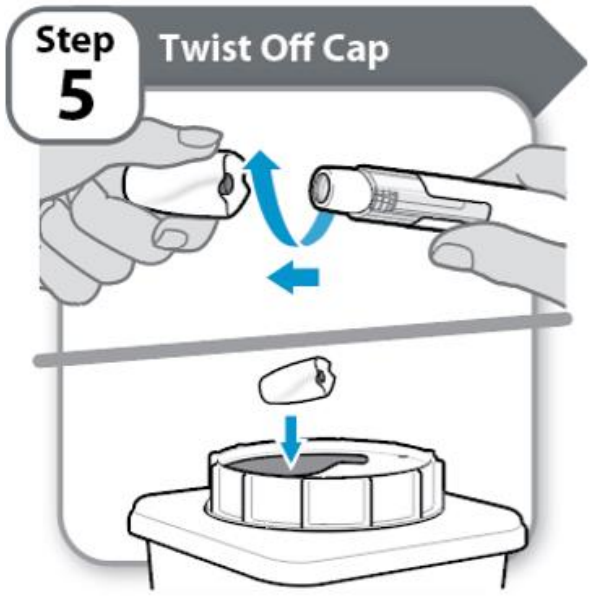
If you have any questions about the medicine, contact your healthcare provider.

Step 4 – Choose and Clean Your Injection Site



- **Choose** an injection site on your stomach area (abdomen) or front of thigh unless a different site has been suggested by your healthcare provider. HYMPAVZI may also be injected into your buttocks by a healthcare provider or caregiver only. Keep at least 2 inches away from your belly button.
- **Change (rotate)** the injection site each time you give yourself an injection of HYMPAVZI and away from any other medicine given under your skin. You may use the same area of your body but be sure to choose a different injection site in that area.
- **Clean** the injection site with soap and water, or an alcohol swab.
- **Allow** the site to air dry. **Do not** touch, fan, or blow on the cleaned injection site.
- **Do not** inject HYMPAVZI into bony areas or areas on your skin that are bruised, red, sore (tender) or hard. Avoid injecting into areas with scars or stretch marks.
- **Do not** inject HYMPAVZI into a vein.
- **Do not** inject HYMPAVZI through your clothes.

Step 5 – Twist Off Cap



- **Twist and pull** off the cap.
- **Put** the cap into an FDA-cleared sharps disposal container right away. You will not need it again.

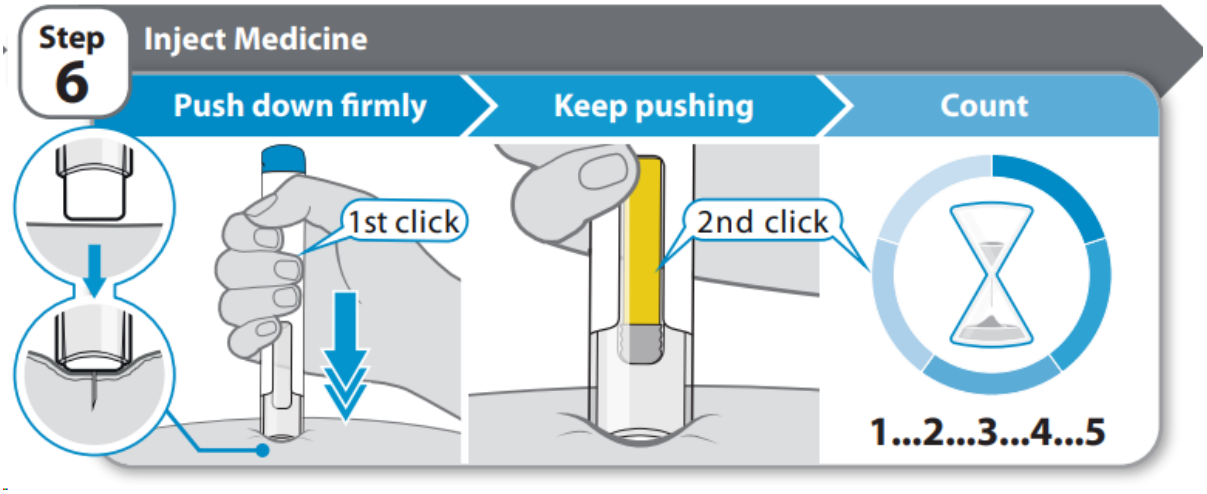
Note:
- It is normal to see a few drops of medicine at the needle tip.
- The needle cover will stay inside the cap after cap removal.

Caution: Handle the Pen with care as it contains a needle.

Do not put or press your hand over the needle guard. Doing so may cause a needle injury.

Injecting HYMPAVZI

Step 6 – Inject Medicine



- **Hold** the Pen straight (at 90° angle) against your clean skin so you can see the window.
- **Push** the Pen **down firmly** straight against your skin and **keep pushing** until the injection is complete. You will hear the **1st click** when the injection starts.
- **Keep pushing** the Pen firmly against your skin while the yellow bar moves across the window. You will hear a **2nd click** when the injection is **almost** complete.
- **Count slowly to 5 after you hear the 2nd click** to make sure you get a full dose.

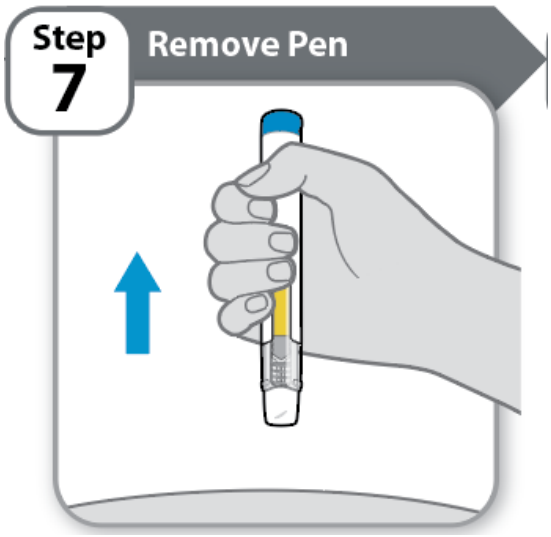
Do not remove the Pen from your skin until you have counted slowly to 5 after you hear the 2nd click and until the yellow marker completely fills the window.

Note: The needle goes into your skin as you push the Pen down. Your healthcare provider may suggest gently pinching your skin while you inject.

Note: If you do not hear a click when pushing the Pen against your skin, try pushing down harder. If you still cannot start the injection, get a new HYMPAVZI Prefilled Pen.

Caution: If you change your mind where to inject after inserting the needle into your skin, you will need to throw away (dispose of) the Pen and get a new HYMPAVZI Prefilled Pen.

Step 7 – Remove Pen

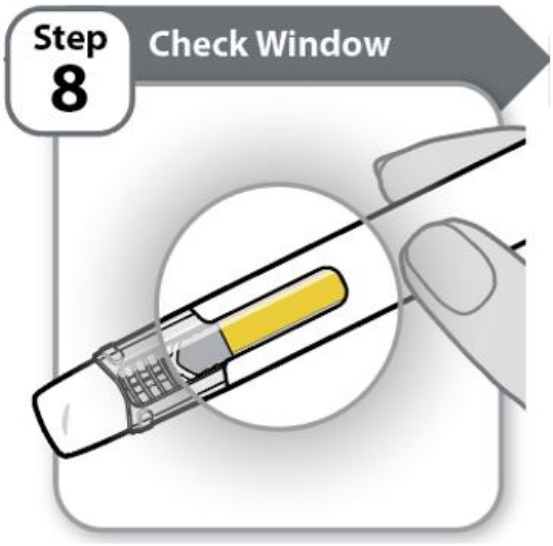


- **Remove** the Pen from your skin.
  - If you see a small drop of medicine on your skin, wait a little longer before removing the Pen when you give your next injection.

Note: After you remove the Pen from your skin, the needle guard will automatically cover the needle and lock in place.

The Pen cannot be reused.

Step 8 – Check Window



- **Check** the window to make sure all the medicine has been injected.

If the yellow bar is not in the position shown, this means you have not received a full dose. Call your healthcare provider for help.

Do not inject another dose.

Step 9 – After Care

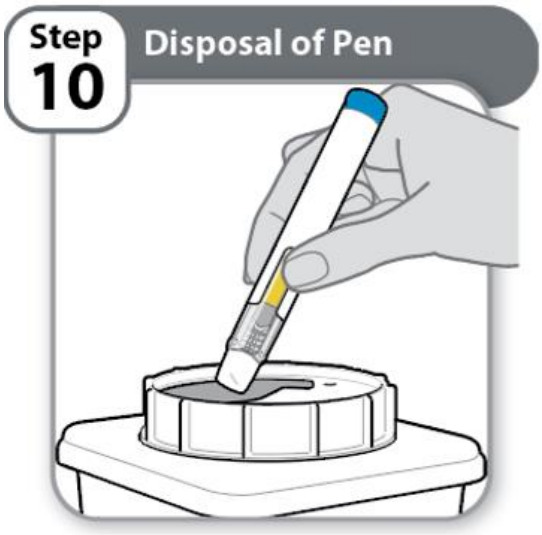


- **Press** lightly on the injection site for a few seconds with a clean cotton ball or gauze pad if you see a drop of blood.
- **Do not** rub the area.

Note: If bleeding does not stop, contact your healthcare provider.

Note: If your prescribed dose requires 2 injections of HYMPAVZI, repeat steps 1-9. Change (rotate) the injection site each time you give yourself an injection of HYMPAVZI. You may use the same area of your body but be sure to choose a different injection site in that area.

Step 10 – Disposal of Pen



- **Put** the used Pen in an FDA-cleared sharps disposal container right away after use.
- **Do not** throw away (dispose of) Pens in the household trash.

Note: If you do not have an FDA-cleared sharps disposal container, please see the "**Safe Pen Disposal**" information section.

Safe Pen Disposal

- **Always throw away** (dispose of) Pens in a sharps disposal container. **Do not** dispose of Pens in the household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that:
  - is made of heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - is upright and stable during use,
  - is leak-resistant, and
  - is properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to throw away (dispose of) your sharps disposal container. There may be state or local laws about how you should throw away used needles and Pens. For more information about safe sharps disposal, and for specific information about safe sharps disposal for the state you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** recycle your used sharps disposal container.

Pfizer

Manufactured by
Pfizer Inc.
New York, NY 10001
US License No. 2001

Distributed by
Pfizer Labs
Division of Pfizer Inc.
New York, NY 10001

LAB-1577-3.0

For more information, go to www.pfizer.com or call 1-800-438-1985.

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: 6/2026

INSTRUCTIONS FOR USE
HYMPAVZI® (him-PAV-zee)
(marstacimab-hncq)
injection, for subcutaneous use
75 mg single-dose prefilled syringe

This Instructions for Use contains information on how to inject HYMPAVZI.

Read this Instructions for Use carefully before using HYMPAVZI Prefilled Syringe and each time there is a refill prescription as there may be new information.

This HYMPAVZI Prefilled Syringe is for use in children 6 to less than 12 years of age and should be given by an adult caregiver only.

Your child's healthcare provider should show a caregiver how to prepare and inject HYMPAVZI before they use it for the first time. **Do not inject anyone until you have been shown how to inject HYMPAVZI.**

Important Information You Need to Know Before Injecting HYMPAVZI

- Each HYMPAVZI Prefilled Syringe is a Single-Dose Prefilled Syringe (called "Syringe" in this Instructions for Use). The HYMPAVZI Prefilled Syringe contains 75 mg of HYMPAVZI for injection under the skin (subcutaneously).
- **Do not** inject HYMPAVZI into a vein.
- To help remember when to inject HYMPAVZI, mark a calendar ahead of time. Call the healthcare provider if you have any questions about the right way to inject HYMPAVZI, or call the helpline at 1-888-496-7289 (1-888 HYMPAV-Z).
- Use HYMPAVZI exactly as prescribed by the healthcare provider.
- HYMPAVZI is not made with natural rubber latex.

Storing HYMPAVZI

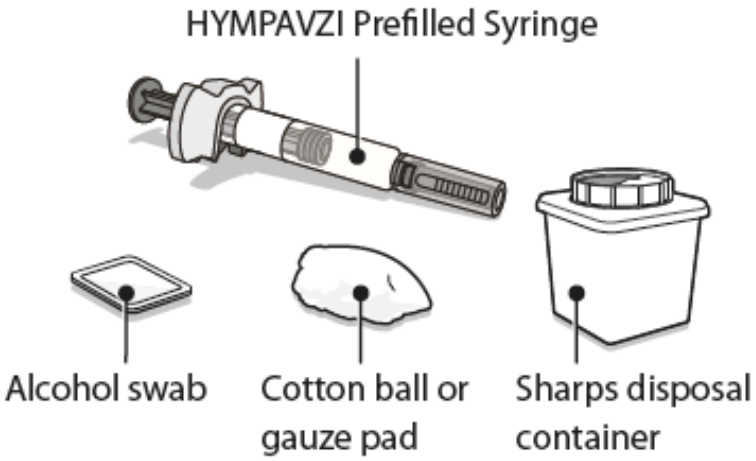
- Store HYMPAVZI in a refrigerator at 36°F to 46°F (2°C to 8°C).
- Store HYMPAVZI in the original carton to protect from light.
- If needed, HYMPAVZI may be stored one time at room temperature, up to 86°F (30°C) in the original carton for up to 7 days. **Do not** return HYMPAVZI to the refrigerator after storing at room temperature.
- Throw away (dispose of) HYMPAVZI that has been left out of the refrigerator for more than 7 days.
- **Do not** freeze HYMPAVZI.
- **Do not** shake HYMPAVZI.
- **Do not** use past the expiration date (Exp) printed on the HYMPAVZI Prefilled Syringe.
- **Keep HYMPAVZI and all medicines out of the reach of children.**

Supplies Needed For HYMPAVZI Injection

Gather the following supplies on a clean flat surface:

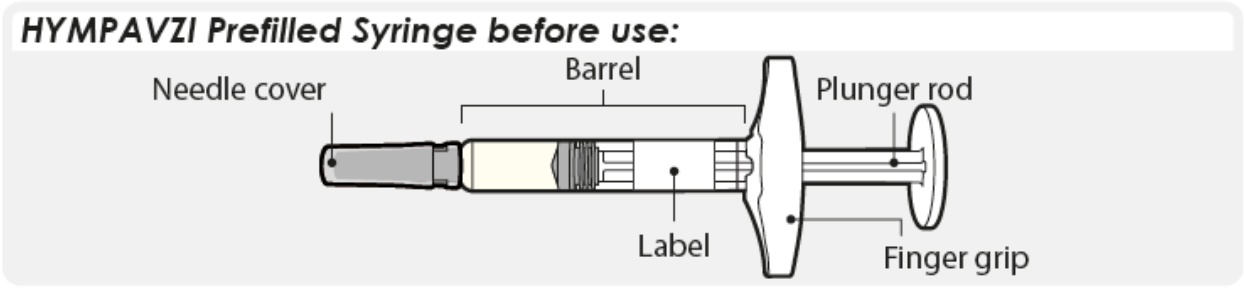
Included in the carton:
- 1 HYMPAVZI Prefilled Syringe

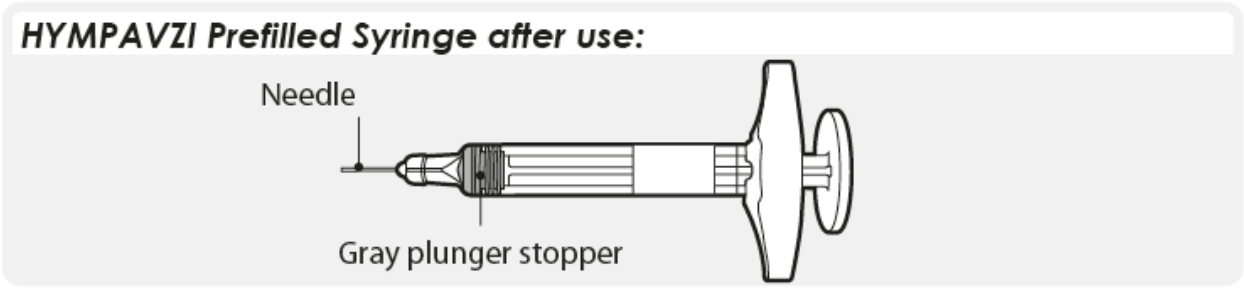
Not included in the carton:
- 1 alcohol swab
- 1 cotton ball or gauze pad
- 1 FDA-cleared sharps disposal container for Syringe disposal (see "**Step 11 - Disposal of Syringe**" and "**Safe Syringe Disposal**" information section)



HYMPAVZI Prefilled Syringe

Always hold HYMPAVZI Prefilled Syringe by the barrel to prevent damage.





Preparing to Inject HYMPAVZI

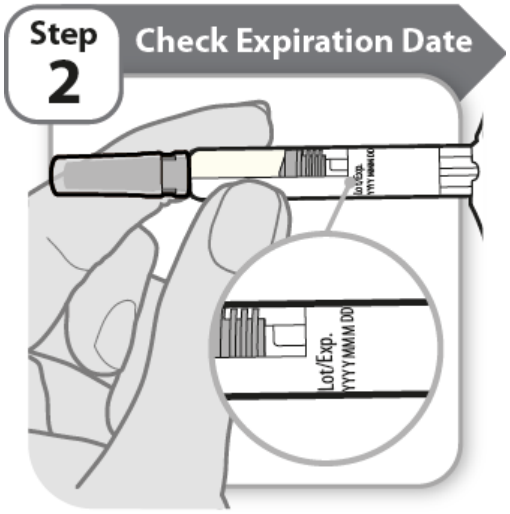
Step 1 – Getting Ready

- **Remove** the Syringe from its carton and keep out of direct sunlight.
- **Make sure** the name HYMPAVZI appears on the carton and Syringe label.
- **Check the Syringe** for any visible damage such as cracks or leaks.
- **Wash and dry** your hands.
- **Do not remove the needle cover until you are ready to inject.**
- **Throw away (dispose of)** the Syringe if it is damaged, or if the Syringe or the carton containing the Syringe has been dropped.
- **Do not** use the Syringe if:
  - it has been stored in direct light. Exposure to room light during dose preparation and injection is acceptable.
  - it has been frozen or thawed, or it has been out of the refrigerator for more than 7 days.

Note: For a more comfortable injection, allow the Syringe to warm at room temperature up to 86°F (30°C) in the carton away from direct sunlight for about 15 to 30 minutes.

Do not use any other methods to warm up the Syringe, such as warming the Syringe in a microwave or hot water.

Step 2 – Check Expiration Date



- **Check** the expiration date (Exp) printed on the Syringe label.
- **Do not** use if the expiration date (Exp) has passed.

Step 3 – Check Medicine

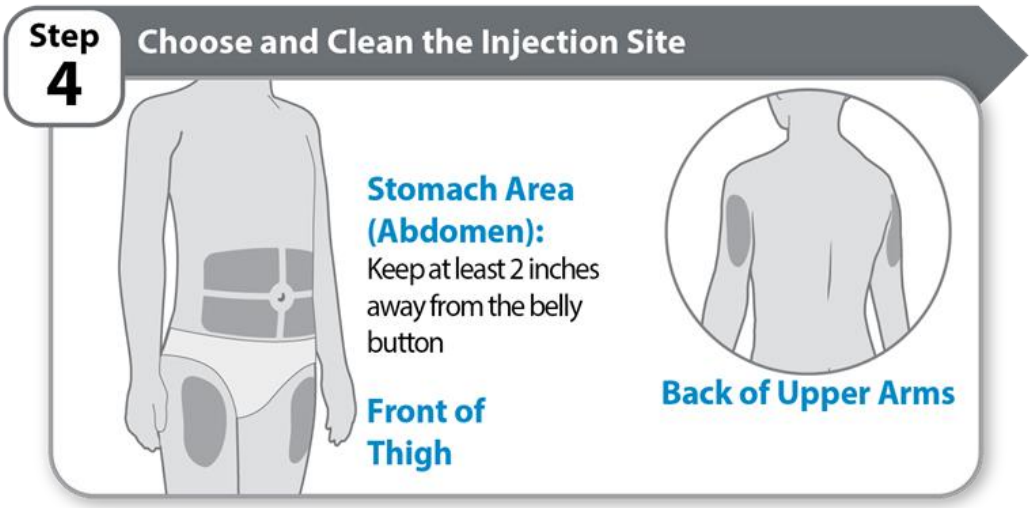


- **Gently** tilt the Syringe back and forth.
- **Look** carefully at the medicine in the Syringe.
  - The medicine should be clear and colorless to light yellow.
  - **Do not** use the Syringe if the medicine is cloudy, dark yellow, or contains flakes or particles.

Note: It is normal to see air bubbles in the Syringe.

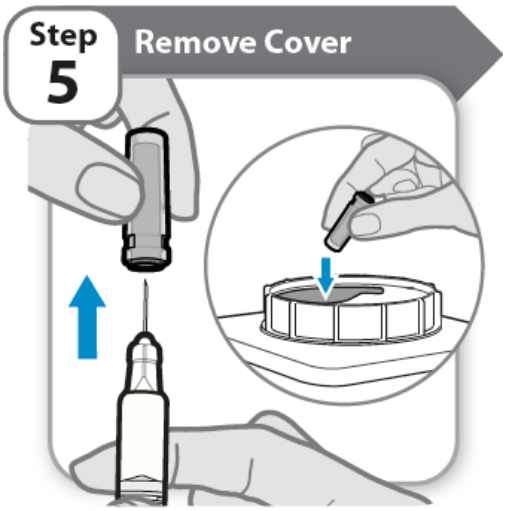
If you have any questions about the medicine, contact the healthcare provider.

Step 4 – Choose and Clean the Injection Site



- **Choose** an injection site on the stomach area (abdomen), front of thigh, or back of upper arms, unless a different site has been suggested by the healthcare provider. Keep at least 2 inches away from the belly button.
- **Change (rotate)** the injection site each time you give an injection of HYMPAVZI and away from any other medicine given under the skin. The same area of the body may be used but be sure to choose a different injection site in that area.
- **Clean** the injection site with soap and water, or an alcohol swab.
- **Allow** the site to air dry. **Do not** touch, fan, or blow on the cleaned injection site.
- **Do not** inject HYMPAVZI into bony areas or areas on the skin that are bruised, red, sore (tender) or hard. Avoid injecting into areas with scars or stretch marks.
- **Do not** inject HYMPAVZI into a vein.
- **Do not** inject HYMPAVZI through clothes.

Step 5 – Remove Cover



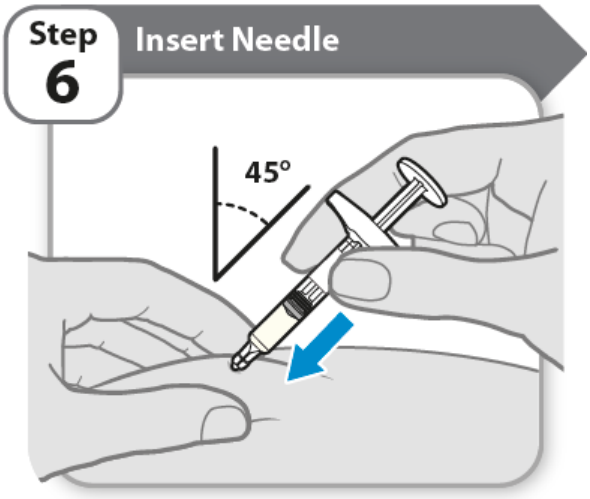
- **Hold** the Syringe by the barrel.
- **Pull** the needle cover straight off carefully.
- **Put** the needle cover into an FDA-cleared sharps disposal container right away. You will not need it again.
- **Do not** touch the needle or let it touch any surfaces.

Note: It is normal to see a few drops of medicine at the needle tip.

Caution: Handle the Syringe with care to avoid an accidental needle injury.

Injecting HYMPAVZI

Step 6 – Insert Needle

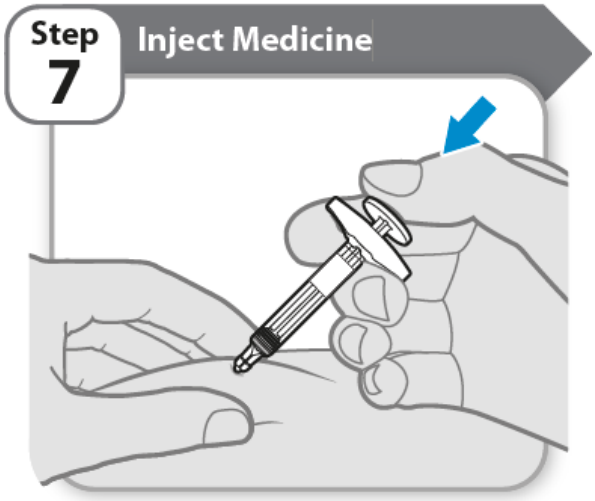


- **Pinch** cleaned skin between your thumb and fingers to create a firm surface.
- **Fully insert** the needle into the skin at a 45° angle, as shown. **Do not** hold or push on the plunger while inserting the needle.

Keep the skin pinched throughout the injection.

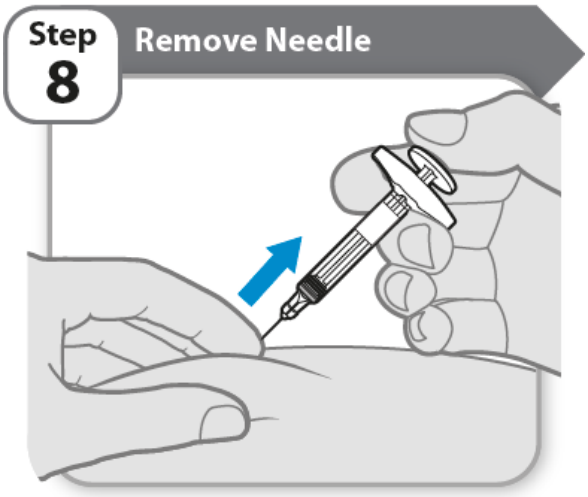
Caution: If you change your mind where to inject after inserting the needle into the skin, you will need to throw away (dispose of) the Syringe and get a new HYMPAVZI Prefilled Syringe.

Step 7 – Inject Medicine



- **Slowly inject** all of HYMPAVZI by gently pushing the plunger rod all the way down, until the barrel is empty.

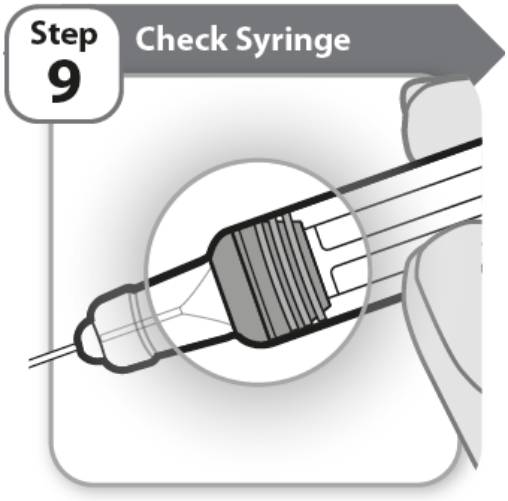
Step 8 – Remove Needle



- **Pull** the needle and Syringe out of the skin at the same angle as inserted.

Note: If you see a small drop of medicine on the skin, wait a little longer before removing the needle when you give the next injection.

Step 9 – Check Syringe



- **Check** the Syringe to make sure the gray plunger stopper is in the position shown.

If the gray plunger stopper is not in the position shown, this means the full dose was not given. Call the healthcare provider for help.

Never re-insert the needle.

Do not inject another dose.

Step 10 – After Care



- **Press** lightly on the injection site for a few seconds with a clean cotton ball or gauze pad if you see a drop of blood.
- **Do not** rub the area.

Note: If bleeding does not stop, contact the healthcare provider.

Note: If the prescribed dose requires 2 injections of HYMPAVZI, repeat steps 1-10. Change (rotate) the injection site each time you give an injection of HYMPAVZI. You may use the same area of the body but be sure to choose a different injection site in that area.

Step 11 – Disposal of Syringe



- **Put** the used Syringe in an FDA-cleared sharps disposal container right away after use.

Never re-cap the needle.

- **Do not** throw away (dispose of) Syringes in the household trash.

Note: If you do not have an FDA-cleared sharps disposal container, please see the **"Safe Syringe Disposal"** information section.

Safe Syringe Disposal

- **Always throw away** (dispose of) Syringes in a sharps disposal container. **Do not** dispose of Syringes in the household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that:
  - is made of heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - is upright and stable during use,
  - is leak-resistant, and
  - is properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to throw away (dispose of) your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about safe sharps disposal for the state you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** recycle your used sharps disposal container.

Pfizer

Manufactured by
Pfizer Inc.
New York, NY 10001
US License No. 2001

Distributed by
Pfizer Labs
Division of Pfizer Inc.
New York, NY 10001

LAB-1626-1.0

For more information, go to www.pfizer.com or call 1-800-438-1985.

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Issued: 6/2026

INSTRUCTIONS FOR USE
HYMPAVZI® (him-PAV-zee)
(marstacimab-hncq)
injection, for subcutaneous use
75 mg single-dose prefilled pen

This Instructions for Use contains information on how to inject HYMPAVZI.

Read this Instructions for Use carefully before using HYMPAVZI Prefilled Pen and each time there is a refill prescription as there may be new information.

This HYMPAVZI Prefilled Pen is for use in children 6 to less than 12 years of age and should be given by an adult caregiver only.

Your child's healthcare provider should show a caregiver how to prepare and inject HYMPAVZI before they use it for the first time. **Do not inject anyone until you have been shown how to inject HYMPAVZI.**

Important Information You Need to Know Before Injecting HYMPAVZI

- Each HYMPAVZI Prefilled Pen is a Single-Dose Prefilled Pen (called "Pen" in this Instructions for Use). The HYMPAVZI Prefilled Pen contains 75 mg of HYMPAVZI for injection under the skin (subcutaneously).
- **Do not** inject HYMPAVZI into a vein.
- To help remember when to inject HYMPAVZI, mark a calendar ahead of time. Call the healthcare provider if you have any questions about the right way to inject HYMPAVZI, or call the helpline at 1-888-496-7289 (1-888 HYMPAV-Z).
- Use HYMPAVZI exactly as prescribed by the healthcare provider.
- HYMPAVZI is not made with natural rubber latex.

Storing HYMPAVZI

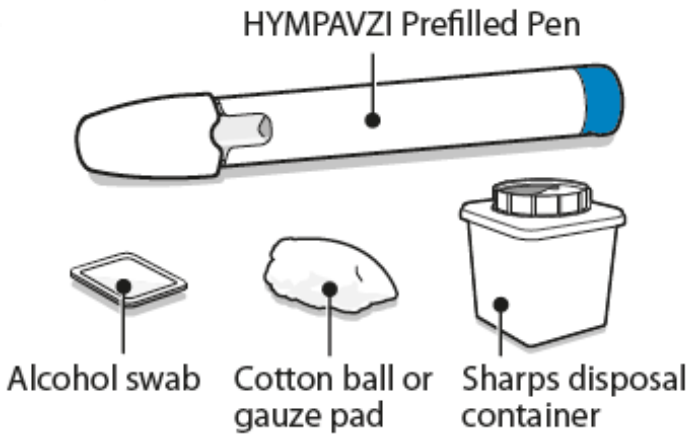
- Store HYMPAVZI in a refrigerator at 36°F to 46°F (2°C to 8°C).
- Store HYMPAVZI in the original carton to protect from light.
- If needed, HYMPAVZI may be stored one time at room temperature, up to 86°F (30°C) in the original carton for up to 7 days. **Do not** return HYMPAVZI to the refrigerator after storing at room temperature.
- Throw away (dispose of) HYMPAVZI that has been left out of the refrigerator for more than 7 days.
- **Do not** freeze HYMPAVZI.
- **Do not** shake HYMPAVZI.
- **Do not** use past the expiration date (EXP) printed on the HYMPAVZI Prefilled Pen.
- **Keep HYMPAVZI and all medicines out of the reach of children.**

Supplies Needed For HYMPAVZI Injection

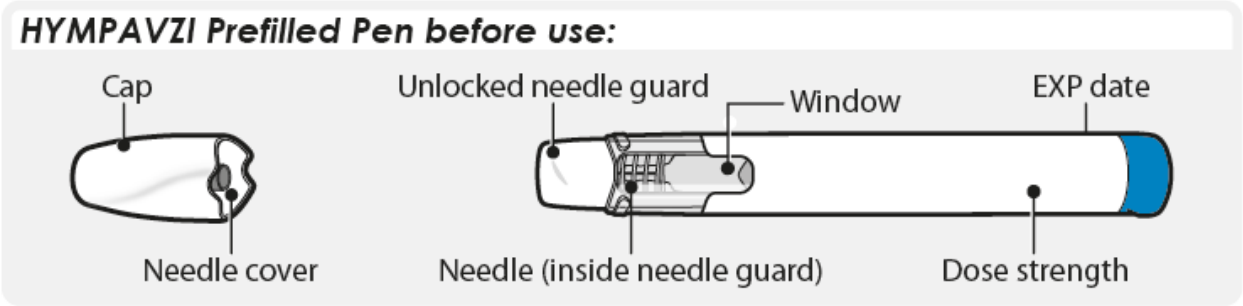
Gather the following supplies on a clean flat surface:

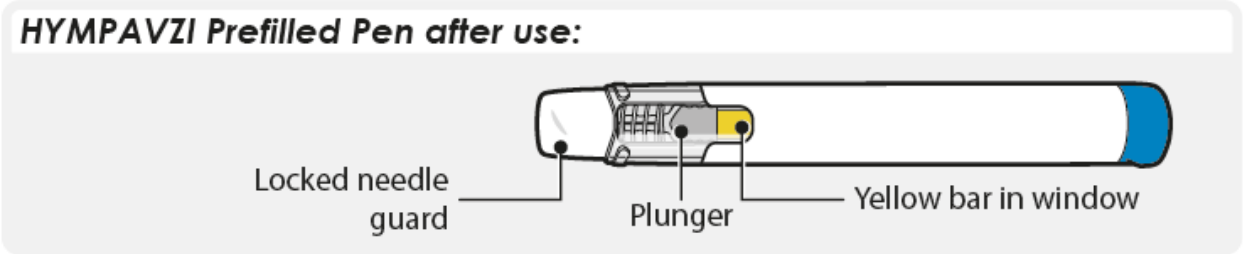
Included in the carton:
- 1 HYMPAVZI Prefilled Pen

Not included in the carton:
- 1 alcohol swab
- 1 cotton ball or gauze pad
- 1 FDA-cleared sharps disposal container for Pen disposal (see "**Step 10 - Disposal of Pen**" and "**Safe Pen Disposal**" information section)



HYMPAVZI Prefilled Pen





Preparing to Inject HYMPAVZI

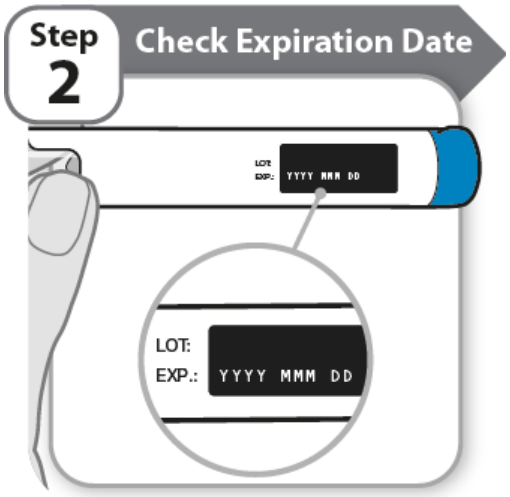
Step 1 – Getting Ready

- **Remove** the Pen from its carton and keep out of direct sunlight.
- **Make sure** the name HYMPAVZI appears on the carton and Pen label.
- **Check the Pen** for any visible damage such as cracks or leaks.
- **Wash and dry** your hands.
- **Do not remove the cap until you are ready to inject.**
- **Throw away (dispose of)** the Pen if it is damaged, or if the Pen or the carton containing the Pen has been dropped.
- **Do not** use the Pen if:
  - it has been stored in direct light. Exposure to room light during dose preparation and injection is acceptable.
  - it has been frozen or thawed, or it has been out of the refrigerator for more than 7 days.

Note: For a more comfortable injection, allow the Pen to warm at room temperature up to 86°F (30°C) in the carton away from direct sunlight for about 15 to 30 minutes.

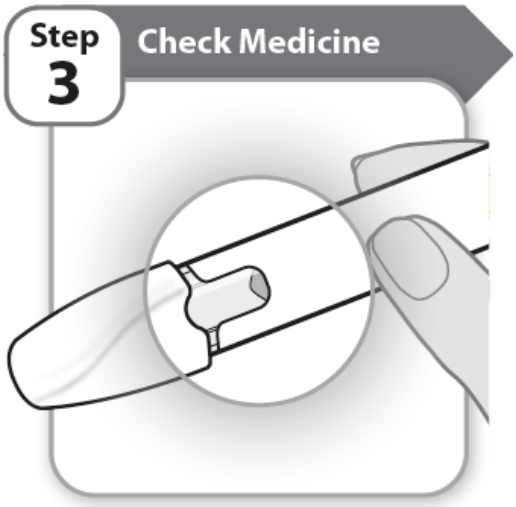
Do not use any other methods to warm up the Pen, such as warming the Pen in a microwave or hot water.

Step 2 – Check Expiration Date



- **Check** the expiration date (EXP) printed on the Pen label.
- **Do not** use if the expiration date (EXP) has passed.

Step 3 – Check Medicine

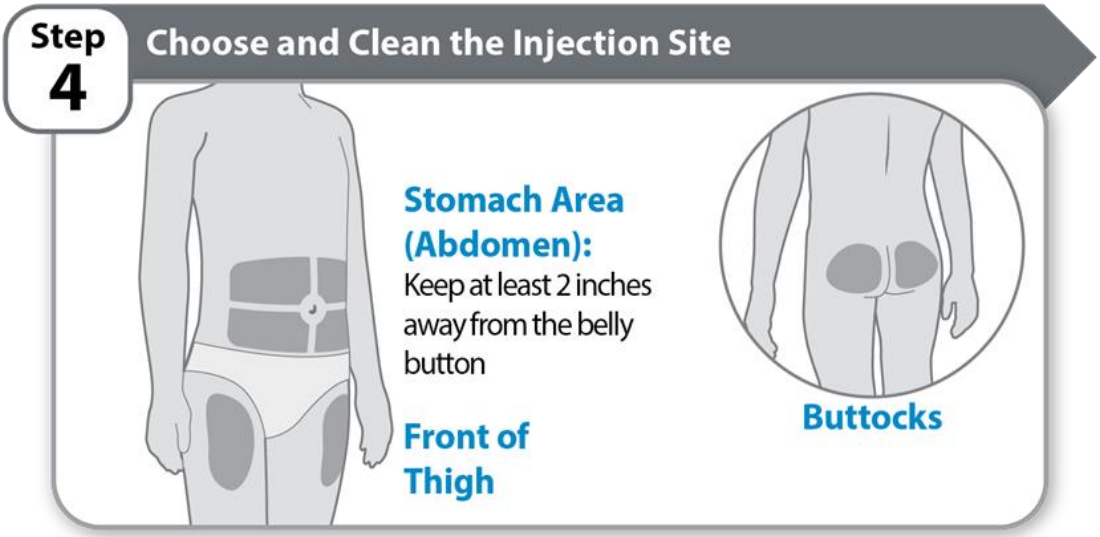


- **Look** carefully at the medicine through the window on the Pen.
  - The medicine should be clear and colorless to light yellow.
  - **Do not** use the Pen if the medicine is cloudy, dark yellow, or contains flakes or particles.

Note: It is normal to see air bubbles in the window.

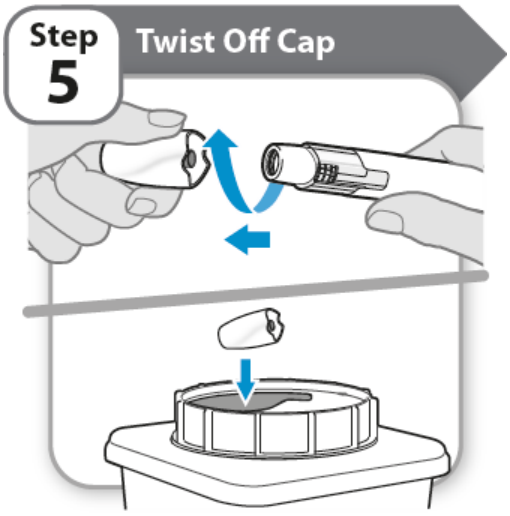
If you have any questions about the medicine, contact the healthcare provider.

Step 4 – Choose and Clean the Injection Site



- **Choose** an injection site on the stomach area (abdomen), front of thigh, or buttocks, unless a different site has been suggested by the healthcare provider. Keep at least 2 inches away from the belly button.
- **Change (rotate)** the injection site each time you give an injection of HYMPAVZI and away from any other medicine given under the skin. The same area of the body may be used but be sure to choose a different injection site in that area.
- **Clean** the injection site with soap and water, or an alcohol swab.
- **Allow** the site to air dry. **Do not** touch, fan, or blow on the cleaned injection site.
- **Do not** inject HYMPAVZI into bony areas or areas on the skin that are bruised, red, sore (tender) or hard. Avoid injecting into areas with scars or stretch marks.
- **Do not** inject HYMPAVZI into a vein.
- **Do not** inject HYMPAVZI through clothes.

Step 5 – Twist Off Cap



- **Twist and pull** off the cap.
- **Put** the cap into an FDA-cleared sharps disposal container right away. You will not need it again.

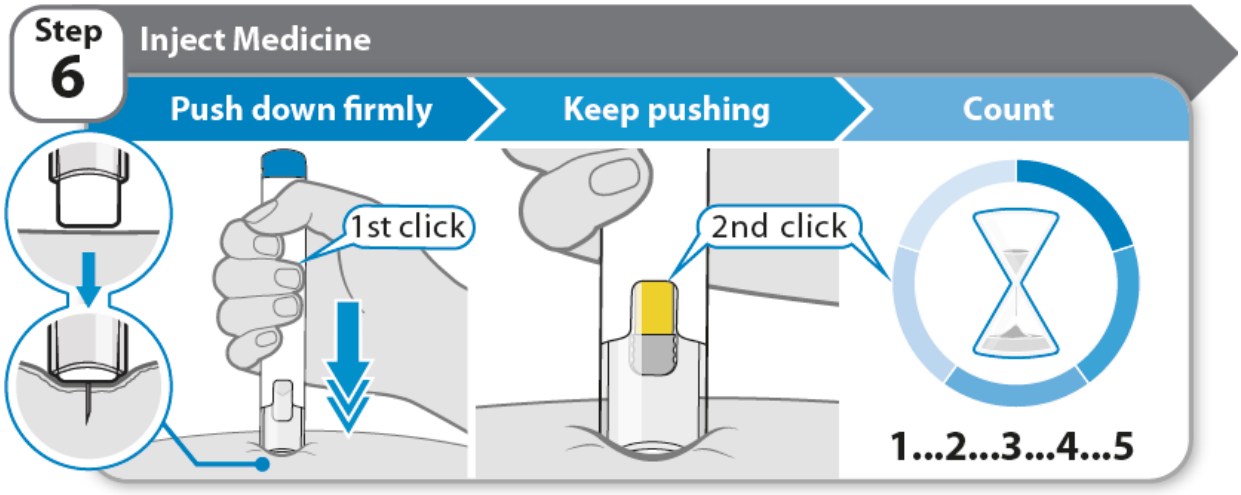
Note:
- It is normal to see a few drops of medicine at the needle tip.
- The needle cover will stay inside the cap after cap removal.

Caution: Handle the Pen with care as it contains a needle.

Do not put or press your hand over the needle guard. Doing so may cause a needle injury.

Injecting HYMPAVZI

Step 6 – Inject Medicine



- **Hold** the Pen straight (at 90° angle) against the clean skin so you can see the window.
- **Push** the Pen **down firmly** straight against the skin and **keep pushing** until the injection is complete. You will hear the **1st click** when the injection starts.
- **Keep pushing** the Pen firmly against the skin while the yellow bar moves across the window. You will hear a **2nd click** when the injection is **almost** complete.
- **Count slowly to 5 after you hear the 2nd click** to make sure the full dose is given.

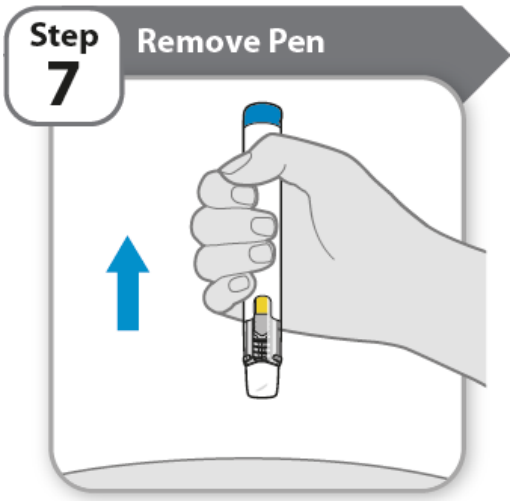
Do not remove the Pen from the skin until you have counted slowly to 5 after you hear the 2nd click and until the yellow marker completely fills the window.

Note: The needle goes into the skin as you push the Pen down. The healthcare provider may suggest gently pinching the skin while you inject.

Note: If you do not hear a click when pushing the Pen against the skin, try pushing down harder. If you still cannot start the injection, get a new HYMPAVZI Prefilled Pen.

Caution: If you change your mind where to inject after inserting the needle into the skin, you will need to throw away (dispose of) the Pen and get a new HYMPAVZI Prefilled Pen.

Step 7 – Remove Pen

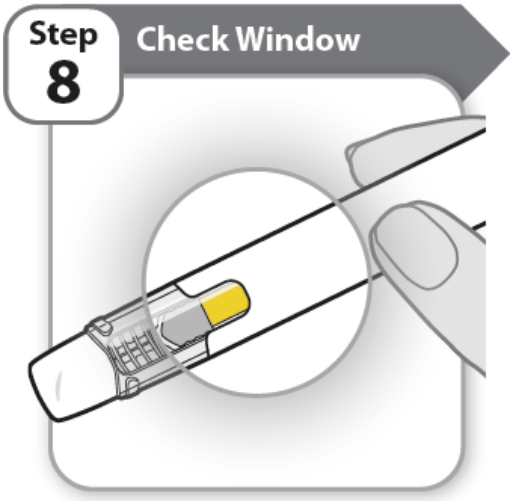


- **Remove** the Pen from the skin.
  - If you see a small drop of medicine on the skin, wait a little longer before removing the Pen when you give the next injection.

Note: After removing the Pen from the skin, the needle guard will automatically cover the needle and lock in place.

The Pen cannot be reused.

Step 8 – Check Window



- **Check** the window to make sure all the medicine has been injected.

If the yellow bar is not in the position shown, this means the full dose was not given. Call the healthcare provider for help.

Do not inject another dose.

Step 9 – After Care

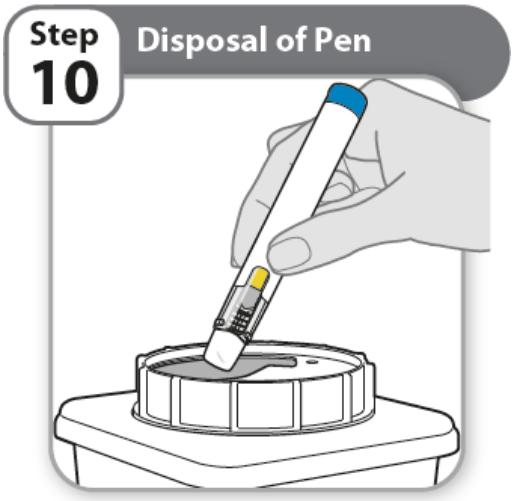


- **Press** lightly on the injection site for a few seconds with a clean cotton ball or gauze pad if you see a drop of blood.
- **Do not** rub the area.

Note: If bleeding does not stop, contact the healthcare provider.

Note: If the prescribed dose requires 2 injections of HYMPAVZI, repeat steps 1-9. Change (rotate) the injection site each time you give an injection of HYMPAVZI. You may use the same area of the body but be sure to choose a different injection site in that area.

Step 10 – Disposal of Pen



- **Put** the used Pen in an FDA-cleared sharps disposal container right away after use.
- **Do not** throw away (dispose of) Pens in the household trash.

Note: If you do not have an FDA-cleared sharps disposal container, please see the **"Safe Pen Disposal"** information section.

Safe Pen Disposal

- **Always throw away** (dispose of) Pens in a sharps disposal container. **Do not** dispose of Pens in the household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that:
  - is made of heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - is upright and stable during use,
  - is leak-resistant, and
  - is properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to throw away (dispose of) your sharps disposal container. There may be state or local laws about how you should throw away used needles and Pens. For more information about safe sharps disposal, and for specific information about safe sharps disposal for the state you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** recycle your used sharps disposal container.

Pfizer

Manufactured by
Pfizer Inc.
New York, NY 10001
US License No. 2001

Distributed by
Pfizer Labs
Division of Pfizer Inc.
New York, NY 10001

LAB-1627-1.0

For more information, go to www.pfizer.com or call 1-800-438-1985.

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Issued: 6/2026

1. 効能・効果

本剤は、以下の疾患を有する成人患者及び 6 歳以上の小児患者における出血傾向の抑制を目的とした定期投与を適応とする。

- 血液凝固第 VIII 因子に対するインヒビターを保有する又は保有しない血友病 A（先天性血液凝固第 VIII 因子欠乏症）、又は
- 血液凝固第 IX 因子に対するインヒビターを保有する又は保有しない血友病 B（先天性血液凝固第 IX 因子欠乏症）

2. 用法・用量

2.1. 成人患者及び 12 歳以上の小児患者における推奨用量

本剤は皮下投与でのみ使用可能である。

成人患者及び 12 歳以上の小児患者に対する本剤の推奨用量は以下の通りである。

負荷用量

300 mg（150 mg を 2 回皮下投与）

全量を投与するために 2 回以上の注射が必要な場合は、投与ごとに部位を変えて投与する。

維持用量

負荷用量投与の 1 週間後に維持用量としての 150 mg 週 1 回皮下投与を開始する。投与は同じ曜日に行うが、投与時刻は問わない。

投与期間中の用量調整

体重 50 kg 以上の患者で出血事象の抑制が不十分と医療従事者が判断した場合には、300 mg 週 1 回皮下投与への増量を検討する。300 mg 週 1 回投与を超える用量で投与したときの本剤の安全性及び有効性は確立されていない。

全量を投与するために 2 回以上の注射が必要な場合は、投与ごとに部位を変えて投与する。

投与忘れ

維持用量として 150 mg を投与している患者の場合：

投与を忘れた場合は、次回投与予定日前に可能な限り速やかに投与し、その後は通常の 150 mg 週 1 回皮下投与（投与忘れ前と同じスケジュール、あるいは忘れた分を投与した日を起点とする新たなスケジュール）を再開する。

直近の投与からの期間が 13 日を超える場合、再開時は負荷用量として 300 mg を皮下投与し、その後は 150 mg 週 1 回皮下投与を再開する。

維持用量として 300 mg を投与している患者の場合：

1 回分以上の投与を忘れた場合は、可能な限り速やかに投与し、その後は 300 mg 週 1 回皮下投与（投与忘れ前と同じスケジュール、あるいは忘れた分を投与した日を起点とする新たなスケジュール）を再開する。

2.2. 6 歳以上 12 歳未満の小児患者における推奨用量

本剤は皮下投与でのみ使用可能である。

6 歳以上 12 歳未満の小児患者に対する本剤の推奨用量は以下の通りである。

負荷用量

150 mg（150 mg を 1 回皮下投与又は 75 mg を 2 回皮下投与）

全量を投与するために 2 回以上の注射が必要な場合は、投与ごとに部位を変えて投与する。

維持用量

負荷用量投与の 1 週間後に維持用量としての 75 mg 週 1 回皮下投与を開始する。投与は同じ曜日に行うが、投与時刻は問わない。

投与期間中の用量調整

体重 25 kg 以上の患者で出血事象の抑制が不十分と医療従事者が判断した場合には、150 mg 週 1 回皮下投与（150 mg を 1 回皮下投与又は 75 mg を 2 回皮下投与）への増量を検討する。6 歳以上 12 歳未満の小児に 150 mg 週 1 回投与を超える用量で投与したときの本剤の安全性及び有効性は確立されていない。

全量を投与するために 2 回以上の注射が必要な場合は、投与ごとに部位を変えて投与する。

投与忘れ

維持用量として 75 mg を投与している患者の場合：

投与を忘れた場合は、次回投与予定日前に可能な限り速やかに投与し、その後は通常の 75 mg 週 1 回皮下投与（投与忘れ前と同じスケジュール、あるいは忘れた分を投与した日を起点とする新たなスケジュール）を再開する。

直近の投与からの期間が 13 日を超える場合、再開時は負荷用量として 150 mg を皮下投与し、その後は 75 mg 週 1 回皮下投与を再開する。

維持用量として 150 mg を投与している患者の場合：

1 回分以上の投与を忘れた場合は、可能な限り速やかに投与し、その後は 150 mg 週 1 回皮下投与（投与忘れ前と同じスケジュール、あるいは忘れた分を投与した日を起点とする新たなスケジュール）を再開する。

2.3. 調製及び投与

- 本剤は医療従事者の指導の下で使用すること。皮下注射について適切な指導を実施したのち、妥当であると医療従事者が判断した場合に、12 歳以上の患者による自己注射及び介護者による投与を行うことができる。

- 本剤の調製及び投与に関する詳細な説明については「使用説明書」を参照のこと。

- 皮下投与する前に本剤を冷蔵庫から取り出し、直射日光を避け、外箱に入れたまま 15～30 分間かけて室温［最大で 86°F（30°C）］に戻しておくこと。熱湯や電子レンジなどの熱源を用いて本剤を温めないこと。本剤を冷蔵庫から取り出した後は 7 日以内に使用すること。7 日以内に使用しなかった場合は廃棄すること*［供給形態／貯法及び取扱い上の注意（16）参照］*。

- 本剤は週 1 回、腹部又は大腿部の前面に皮下注射する。投与時刻は問わない。必要な場合はその他の部位への投与も許容される。上腕部の後面（プレフィルドシリンジのみ）及び臀部（プレフィルドペン型注入器のみ）への投与は介護者又は医療従事者のみが行う。骨ばった部位や内出血、発赤、圧痛、硬結、瘢痕又は伸展裂創などが認められる部位には投与しないこと。静脈内への投与は行わないこと。投与ごとに投与部位を変えること。

- 本剤による治療期間中に他の製剤の皮下投与を行う場合は、異なる部位に投与することが望ましい。

- 注射用医薬品は、溶液や容器の確認が可能な場合、投与前に目視で粒子状物質及び変色がないか確認すること。本剤は澄明で無色～淡黄色の溶液である。溶液中に濁り、濃い黄色の変色又は薄片や微粒子が認められる場合は使用しないこと。

2.4. 本剤への切り替え

血液凝固因子補充療法又はバイパス止血製剤から本剤に切り替える場合：本剤の投与を開始する前に血液凝固因子製剤（血液凝固第 VIII 因子又は血液凝固第 IX 因子製剤）又はバイパス止血製剤［例：遺伝子組み換え第 VIIa 因子製剤（rFVIIa）又は活性型プロトロンビン複合体製剤（aPCC）］の投与を中止すること。血液凝固因子製剤又はバイパス止血製剤の中止後はいつでも本剤の投与を開始することができる。

他の血液凝固因子製剤以外の血友病治療薬から本剤に切り替えた場合の患者におけるデータは得られていない。

2.5. 出血の治療に関するガイダンス

血液凝固第 VIII 因子製剤及び血液凝固第 IX 因子製剤又はバイパス止血製剤（例：rFVIIa 又は aPCC）は、本剤の投与を受けている患者での出血の治療薬として投与することが可能である。出血の治療を目的とした本剤の追加的投与は行わないこと。必要な場合は、すべての患者及び（又は）介護者に対して、本剤の予防的投与の実施中に使用する血液凝固因子製剤又はバイパス止血製剤の用量及び投与スケジュールについて、説明すること。

血液凝固第 VIII 因子製剤若しくは血液凝固第 IX 因子製剤又はバイパス止血製剤により出血を治療する場合、これらの製剤の添付文書に従って最小有効量を用いることが推奨される*［警告及び使用上の注意（5.1）参照］*。使用する血液凝固因子製剤又はバイパス止血製剤の添付文書全文を参照すること。rFVIIa の場合は、最高用量として 90 mcg/kg 体重／回、最高投与頻度として 2 時間ごとが推奨される。aPCC の場合は、最高用量として 100 単位／kg 体重の 24 時間以内の投与が推奨される。

2.6. 外科的処置又はその他の介入処置のための一時的中断

周術期の管理

大手術における本剤の評価は実施していない。臨床試験において、患者は小手術を受ける際に本剤の予防的投与を中止しなかった。

大手術を行う場合は少なくとも 7 日前から本剤の投与を中断し、血液凝固因子製剤又はバイパス止血製剤を用いた各国の標準治療に基づく管理を開始し、周術期に上昇する可能性のある静脈血栓症のリスクを管理するための措置を行うことが推奨される。大手術を受ける血友病患者に血液凝固因子製剤又はバイパス止血製剤を投与する際は、当該製剤の製品情報をガイドラインとして参照すること。本剤の投与を再開する場合は、術後の血栓塞栓症危険因子の有無や、その他の止血製剤及び併用薬の使用を含めて、患者の全身状態を考慮すること*［用法・用量（2.1）参照］*。

急性の重度疾患を有する患者の管理

急性の重度疾患を有する患者での本剤の使用経験は限られている。本剤の投与の一時的な中断を検討する理由になるものとして、血液凝固の活性化を増大させ、本剤の投与に伴うリスクを高める可能性があると医療従事者が判断した急性の重度疾患（重篤な感染症、敗血症、外傷など）が挙げられる。急性の重度疾患の治療は各国の標準治療に従って行うこととし、本剤の投与を継続する場合は、投与に伴う潜在的リスクを比較検討した上で行う。本剤の投与は患者が臨床的に回復してから再開する*［用法・用量（2.1）参照］*。

2.7. 妊娠検査

妊娠可能な女性には、妊娠していないことを確認してから本剤の投与を開始する*［警告及び使用上の注意（5.3）、特定の集団への投与（8.1、8.3）参照］*。

2.8. 免疫寛容導入療法

インヒビター根絶のための脱感作療法である免疫寛容導入療法（ITI）を継続中の患者における本剤の安全性及び有効性は確立されておらず、データは得られていない。ITI 中の本剤の継続又は開始を検討する場合は、潜在的なベネフィットとリスクを慎重に評価すること。

3. 剤形及び含量

本剤（マルスタシマブ-hncq）は澄明で無色～淡黄色の溶液であり、下記の剤形で入手可能である。

プレフィルドシリンジ

- 注射液：150 mg/mL を含有する単回投与用プレフィルドシリンジ
- 注射液：75 mg/0.5 mL を含有する単回投与用プレフィルドシリンジ

プレフィルドペン型注入器

- 注射液：150 mg/mL を含有する単回投与用プレフィルドペン型注入器
- 注射液：75 mg/0.5 mL を含有する単回投与用プレフィルドペン型注入器

4. 禁忌

なし。

5. 警告及び使用上の注意

5.1. 血栓塞栓性事象

本剤は組織因子経路インヒビター（TFPI）拮抗薬であり、血栓塞栓性合併症のリスクを増大させる可能性がある。非盲検継続投与試験において本剤投与を受けた患者の 0.8%（2/259 例）で静脈及び動脈血栓塞栓性事象が報告された*［副作用（6.1）参照］*。

血栓塞栓性事象の独立した危険因子を有する患者においては、本剤の使用により血栓塞栓性事象のリスクが増加する可能性がある。

血栓塞栓性事象の既往歴を有する患者を対象としたマルスタシマブの臨床試験は実施していない*［臨床試験（14.1）参照］*。血栓塞栓症の既知の危険因子を有する患者においては、本剤の使用に関する有益性とリスクを考慮すること。

血栓塞栓症を示す診断所見が認められた場合は本剤の予防的投与を中断し、臨床的必要性に応じて管理すること。

本剤の予防的投与を受けている患者に血液凝固第 VIII 因子製剤若しくは血液凝固第 IX 因子製剤又はバイパス止血製剤を使用する場合は、これらの製剤の添付文書に従って最小有効量を用いることが推奨される*［用法・用量（2.5）参照］*。

5.2. 過敏症

本剤は過敏症反応（蕁麻疹及びそう痒症を含むがこれらに限らない）を引き起こすことがある。本剤を投与した患者で重度の過敏症反応が認められた場合は、本剤の投与を中止して直ちに救急治療を受けるよう指導する。

5.3. 胚・胎児毒性

本剤の作用機序に基づくと、本剤を妊婦に投与した場合、胎児に有害な作用を及ぼす可能性がある*［臨床薬理（12.1）参照］*。妊婦には、胎児への潜在的リスクについて説明すること。妊娠可能な女性には、本剤の投与期間中及び最終投与後 2 カ月間は効果の高い避妊法を使用するように助言する*［特定の集団への投与（8.1、8.3）参照］*。

5.4. フィブリン D ダイマー及びプロトロンビンフラグメント 1.2 の臨床検査値上昇

その作用機序及び止血効果と一致して、本剤はフィブリン D ダイマー及びプロトロンビンフラグメント 1.2 を上昇させる*［臨床薬理（12.1、12.2）参照］*。これらのバイオマーカーの生理的な値を超える散発性又は一過性の上昇が報告されているが、それに伴う安全性の懸念は認められていない*［臨床薬理（12.2）参照］*。6 歳から 18 歳未満の小児患者 10 例（8.1%）及び成人患者 6 例（4.4%）でフィブリン D ダイマー値の上昇が認められた。6 歳から 18 歳未満の小児患者 13 例（10.5%）及び成人患者 6 例（4.4%）でプロトロンビンフラグメント 1.2 値の上昇が認められた。本剤投与中の患者では、このような凝固バイオマーカーは、深部静脈血栓症（DVT）及び肺塞栓症（PE）などの血栓症が疑われる場合の臨床的判断の際の信頼性のある予測マーカーとならない可能性がある。

6. 副作用

以下の臨床的に意味のある副作用は、本文書の別項に詳細を記載した。

- 血栓塞栓性事象*［警告及び使用上の注意（5.1 参照）］*
- 過敏症*［警告及び使用上の注意（5.2 参照）］*

6.1. 臨床試験での使用経験

臨床試験はさまざまな条件下で実施されるため、ある薬剤の臨床試験で認められた副作用の発現割合を別の薬剤の臨床試験での発現割合と直接比較することはできない。また、臨床試験で認められた副作用の発現割合は、臨床現場での発現割合を反映していない可能性がある。

BASIS 試験及び BASIS KIDS 試験に組み入れたインヒビターを保有する又は保有しない重症血友病 A（血液凝固第 VIII 因子が 1%未満）又は中等症から重症の血友病 B（血液凝固第 IX 因子が 2%以下）の成人患者及び 6 歳以上の小児患者を対象に、マルスタシマブの安全性を評価した。患者 259 例にマルスタシマブの予防的投与として推奨される負荷用量を皮下投与し、その後第 8 日から維持用量を週 1 回皮下投与した*［臨床試験（14.1、14.2、14.3）参照］*。135 例（52%）が成人（18 歳以上）、56 例（22%）が青年（12～18 歳未満）、68 例（26%）が小児（6～12 歳未満）であった。マルスタシマブの投与を受けた患者の 90%が 6 カ月以上投与を継続し、82%が 1 年以上投与を継続した。試験全体で投与期間の中央値は 364 日（最小値、最大値：14、406 日）であった。

マルスタシマブの予防的投与を受けたすべての年齢群の患者の 2%以上で報告された副作用を Table 1 に要約する。

Table 1　　マルスタシマブの投与を受けた患者の 2%以上で報告された副作用（年齢群別）*

副作用	6～18 歳未満の患者数 n (%) (N = 124)	18 歳以上の患者数 n (%) (N = 135)	患者数（全年齢群） n (%) (N = 259)
注射部位反応**	19 (15)	11 (8)	30 (12)
頭痛***	9 (7)	10 (7)	19 (7)
発熱	12 (10)	3 (2)	15 (6)
関節痛	4 (3)	5 (4)	9 (3)
下痢	5 (4)	2 (2)	7 (3)
そう痒症	1 (1)	5 (4)	6 (2)
発疹	2 (2)	3 (2)	5 (2)

*BASIS 試験及び BASIS KIDS 試験の 12 カ月の実薬投与期間に得られたデータ
**注射部位反応は以下の用語を含むグループ用語である：注射部位そう痒感、注射部位腫脹、注射部位紅斑、注射部位内出血、注射部位硬結、注射部位疼痛、注射部位浮腫、注射部位血腫、注射部位出血、注射部位熱感及び注射部位蕁麻疹。
*** 頭痛は片頭痛を含むグループ用語である。

非盲検延長試験において、本剤を投与された患者の 0.9%（1/116 例）に静脈血栓症の重篤な有害事象が発現した*［臨床試験（14.1）参照］*。

7. 薬物相互作用

部分トロンボプラスチン時間（aPTT）及びプロトロンビン時間（PT）

マルスタシマブの投与後、活性化部分トロンボプラスチン時間（aPTT）及びプロトロンビン時間（PT）を含む凝固検査の基準値に臨床的に意味のある差は認められなかった。

8. 特定の集団への投与

8.1. 妊婦

リスクの要約

作用機序に基づくと、本剤を妊婦に投与した場合、胎児に有害な作用を及ぼす可能性がある*［臨床薬理（12.1）参照］*。妊婦での本剤の使用に関して、投与に伴う重大な先天異常、流産又はその他の母親若しくは胎児における有害な転帰のリスクを評価するためのデータは得られていない。雌動物を用いたマルスタシマブの生殖発生毒性試験は実施していない。本剤に関するデータはないが、モノクローナル抗体は能動的に輸送され胎盤を通過することから、マルスタシマブは胎児に有害な作用を及ぼす可能性がある。

対象集団における重大な先天異常及び流産の背景リスクは不明である。すべての妊娠には、先天異常、胎児死亡又はその他の有害な転帰の背景リスクが存在する。米国の一般集団では、臨床的に確認された妊娠における重大な先天異常及び流産の背景リスクの推定値は、それぞれ 2%～4%及び 15%～20%である。

8.2. 授乳婦

リスクの要約

ヒト又は動物の乳汁中へのマルスタシマブの移行の有無、授乳児への影響又は乳汁産生への影響に関するデータは得られていない。

母体由来の IgG 及びモノクローナル抗体はヒト乳汁中に移行することが知られている。マルスタシマブがヒト乳汁中に移行した場合の、母乳を摂取した乳児におけるマルスタシマブの局所的な消化管曝露及び限定的な全身曝露の影響は不明である。

授乳の発育上及び健康上の有益性を、母親による本剤の臨床的必要性並びに本剤又は母親の背景から生じる可能性のある授乳児への有害作用と合わせて考慮する必要がある。

8.3. 生殖能を有する女性及び男性

本剤を妊婦に投与した場合、胎児に有害な作用を及ぼす可能性がある*［特定の集団への投与（8.1）参照］*。

妊娠検査

妊娠可能な女性には、妊娠の有無を確認してから本剤の投与を開始する。

避妊

女性

妊娠可能な女性患者には、本剤の投与期間中及び最終投与後 2 カ月間は効果の高い避妊法を使用するように助言する。

8.4. 小児への投与

インヒビターを保有する又は保有しない血友病 A 又は B を有する患者の出血傾向の抑制における本剤の安全性及び有効性は、6 歳以上の小児患者では確立されている*［臨床試験（14.1、14.2、14.3）参照］*。この適応での小児患者における本剤の使用は、非盲検、多施設共同試験 2 試験（BASIS 試験及び BASIS KIDS 試験）で得られたデータによって支持されている。これら 2 試験では 56 例の青年（12～18 歳未満）が投与を受けた。BASIS KIDS 試験では 68 例の小児（6～12 歳未満）が投与を受けた。有効性及び副作用プロファイルは小児患者及び成人患者間で同程度であった*［副作用（6.1）及び臨床試験（14.1、14.2、14.3）参照］*。小児患者と成人患者間で認められた定常状態時の薬物動態（PK）上の曝露量の差は主に体重によるものであった*［臨床薬理（12.3）参照］*。

6 歳未満の小児患者における本剤の安全性及び有効性は確立されていない。

8.5. 高齢者への投与

インヒビターを保有する又は保有しない血友病 A 又は B を対象とした臨床試験に組み入れられた 65 歳以上の患者は 2 例であった*［臨床試験（14.1、14.2）参照］*。本剤の臨床試験には十分

な数の 65 歳以上の患者が組み入れられていないため、高齢患者が若年患者と異なる反応を示す否かは判断できない。

ANNEX I

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
Hympavzi 150 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Hympavzi 150 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 150 mg marstacimab in 1 mL of solution.

Hympavzi 150 mg solution for injection in pre-filled pen

Each pre-filled pen contains 150 mg marstacimab in 1 mL of solution.

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

Excipients with known effect

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:

- Haemophilia A (congenital factor VIII deficiency):
  - Without factor VIII inhibitors who have severe disease (FVIII < 1%)
  - With factor VIII inhibitors
- Haemophilia B (congenital factor IX deficiency):
  - Without factor IX inhibitors who have severe disease (FIX < 1%)
  - With 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 serious infection, sepsis, trauma, crush injuries, and cancer, 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

For patients on a maintenance dose of 150 mg
If a dose is missed, the missed dose should be administered as soon as possible before the day of the next scheduled dose, and then usual 150 mg subcutaneous weekly dosing schedule (same schedule as prior to the missed dose or new schedule based on date of administration of missed dose) should be resumed.

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.

For patients on a maintenance dose of 300 mg
If one or more doses are missed, the missed dose should be administered as soon as possible, and then the usual 300 mg subcutaneous weekly dosing schedule (same schedule as prior to the missed dose or new schedule based on date of administration of missed dose) should be resumed.

Switching to Hympavzi
Switching from prophylactic factor replacement therapy or bypassing agents to Hympavzi: Prior to initiation of Hympavzi, patients should discontinue treatment with clotting factor concentrates (factor VIII or factor IX concentrates) or bypassing agents (e.g. recombinant FVIIa [rFVIIa] or activated prothrombin complex concentrate [aPCC]). Patients can initiate Hympavzi at any time after discontinuing clotting factor concentrates or bypassing agents.

Switching from non-factor-based haemophilia medicinal products to Hympavzi: No clinical study data are available to guide converting patients from other 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 or bypassing agents 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 pause Hympavzi at least 7 days prior and initiate management per local standard of care with clotting factor concentrate or bypassing agent 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 or bypassing agent should be consulted for dosing 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).

Immune tolerance induction (ITI)
The safety and efficacy of marstacimab in patients receiving ongoing ITI have not been established, and no data are available.

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. Arterial and 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).
- patients managed in perioperative setting and/or undergoing surgery (see section 4.2). In the perioperative setting, concomitant use of Hympavzi with other haemostatic agents can potentially increase the risk of thrombosis.

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 benefits and risks 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 prophylactic 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 patients should be managed as clinically indicated.

The use of anti-tissue factor pathway inhibitor (anti-TFPI) products, including marstacimab, 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 and bypassing agents have been safely administered for the treatment of breakthrough bleeds in patients receiving marstacimab. If factor VIII or factor IX products or bypassing agents are indicated in a patient receiving Hympavzi prophylaxis, the minimum effective dose according to the product label is recommended. Patients should be informed of and monitored for the occurrence of signs and symptoms of thromboembolic events. In case of suspicion of thromboembolic events, Hympavzi should be discontinued and appropriate medical treatment should be initiated.

Guidance on treating breakthrough bleeds

Factor VIII and factor IX products or bypassing agents (e.g. rFVIIa or aPCC) 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 the clotting factor concentrates or bypassing agents to use, if required, while receiving Hympavzi prophylaxis.

When treating breakthrough bleeds with factor VIII or factor IX products or with bypassing agents, the lowest effective dose according to the product prescribing information is recommended. Healthcare professionals should refer to the product information for the clotting factor concentrate or bypassing agent being used. For rFVIIa, a maximum dose of 90 µg/kg body weight per dose and a maximum dosing frequency of every 2 hours is recommended. For aPCC, a maximum dose of 100 units/kg body weight within 24 hours is recommended.

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.

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.

Nonclinical in vitro pharmacodynamic drug interaction studies were conducted and support the concomitant use of marstacimab with bypassing agents (e.g. rFVIIa or aPCC) for treatment of breakthrough bleeds. Combination of marstacimab with rFVIIa or aPCC (in haemophilia A and B plasma with inhibitors) resulted in increased thrombin generation compared to marstacimab treatment alone without exceeding peak thrombin levels achieved in non-haemophilic plasma treated with marstacimab alone; in some cases thrombin levels were within the range reported for non-haemophilic normal plasma.

Nonclinical in vivo pharmacodynamic drug interaction studies conducted in rats with normal FVIII and FIX levels also support the concomitant use of marstacimab with rFVIIa at a maximum clinical dose of ≤ 90 µg/kg or with aPCC at a maximum clinical dose of 100 units/kg for treatment of breakthrough bleeds. Increased incidence and/or severity of acute thrombi/emboli in the lung and injection site were observed in haemostatically normal rats at higher doses of rFVIIa (see section 5.3).

For guidance on the use of clotting factor concentrates or bypassing agents for treatment of breakthrough bleeds in patients receiving marstacimab prophylaxis, see section 4.4.

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 pooled data from clinical studies. The most serious adverse drug reaction reported from the clinical studies with marstacimab was thrombosis (0.6%) (see section 4.4).

The most frequently reported adverse reactions after treatment with marstacimab were injection site reactions (ISRs) (11.4%).

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 from the patients who rolled over from the BASIS study into the 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 167 male patients with haemophilia A or B with inhibitors (30.5%) or without inhibitors (69.5%) to marstacimab administered once weekly. Of the 167 patients, 135 (80.8%) were adults (18 years of age and older) and 32 (19.2%) were adolescents (12 years up to < 18 years). A total of 154 of the 159 patients completing the 12-month treatment period subsequently enrolled in the ongoing OLE study. The median total duration of exposure was 1 225 days (range 28 to 1 659 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[a]	Common
Vascular disorders	Hypertension Thromboembolic events (thrombosis[b])	Common Uncommon
Skin and subcutaneous tissue disorders	Rash[c] Pruritus	Common Common
General disorders and administrations site conditions	Injection site reactions[c]	Very common

a. Headache includes both headache and migraine.
b. ADR reported in the open-label extension study.
c. see 'Description of selected adverse reactions'

Description of selected adverse reactions

Injection site reactions
In total, 19 (11.4%) 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 haemorrhage, injection site induration, injection site oedema, injection site pain, injection site pruritus, and injection site swelling.

Rash
In total, 6 (3.6%) patients treated with marstacimab reported rash.

One patient with severe haemophilia B with inhibitors and a history of allergic reaction to exogenous factor IX experienced severe rash with onset at approximately 9 months. The patient required a prolonged course of oral corticosteroids for resolution and treatment with marstacimab was discontinued.

Paediatric population

The paediatric population studied comprises a total of 32 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 national reporting system listed in Appendix V.

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 with and without inhibitors 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.

There were no clinically relevant differences in pharmacodynamic effects between haemophilia participants with and without inhibitors following weekly subcutaneous administration of marstacimab.

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 which included a non-inhibitor cohort of 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 non-inhibitor cohort 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 36.4% had 3 or more target joints at study entry. In the routine prophylaxis cohort, 55.4% 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 non-inhibitor cohort 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 (Non-inhibitor cohort)

In the OLE of the pivotal Phase 3 study, 107 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 43 months (mean 31 months) where marstacimab was shown to maintain long-term 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 during OLE Study B7841007*			
	Year 1 (N = 107)	**Year 2 (N = 103)**	**≥ Year 3 (N = 96)**	**Overall (N = 107)**
Treated bleeds				
Mean ABR (95% CI)	3.17 (2.32, 4.32)	2.53 (1.87, 3.43)	1.81 (1.31, 2.52)	2.95 (2.21, 3.94)
Median ABR (IQR)	1.00 (0.00, 5.00)	1.00 (0.00, 3.00)	0.00 (0.00, 2.66)	0.94 (0.35, 4.40)

*Patients received marstacimab for up to an additional 43 months (mean 31 months) during B7841007.

Year 1: Day 1 to Day 365; Year 2: Day 366 to Day 730; ≥ Year 3: Day 731 to the 43-month data cut-off

- 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 come from the descriptive summary.
- ABR = Annualised Bleeding Rate; CI = Confidence Interval; IQR = Interquartile Range; N = number of patients who contributed data for analyses at each time interval

Clinical studies in adult and adolescent patients with haemophilia A with FVIII inhibitors or haemophilia B with FIX inhibitors

Patients (aged ≥ 12 years old and ≥ 35 kg) with haemophilia A with inhibitors and haemophilia B with inhibitors (Study B7841005)

The pivotal Phase 3 study was a one-way, cross-over, open-label, multi-centre study which included an inhibitor cohort of 51 adult and adolescent males (aged 12 years and older and ≥ 35 kg) with severe haemophilia A with FVIII inhibitors or severe haemophilia B with FIX inhibitors who previously received on-demand (N = 48) or prophylactic (N = 3) treatment with bypassing agents (rFVIIa or aPCC). All patients had a documented history of inhibitors. 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.

After the 6-month Observational Phase, 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. Four (7.8%) out of 51 patients who received marstacimab for at least 6 months underwent dose escalation of their maintenance dose.

The primary efficacy objective of the study was to compare marstacimab prophylaxis during the Active Treatment Phase versus on-demand bypassing agent 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 on-demand bypassing agent 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).

Among the 51 patients treated with marstacimab (78.4% haemophilia A, 21.6% haemophilia B), the mean age was 27.7 years (min 12, max 75); 25.5% of patients were 12 to < 18 years, 74.5% were ≥ 18 years, 100% were male. In this inhibitor cohort, 29.4% of patients were White, 54.9% were Asian, 15.7% were Black or African American, and 2.0% of patients identified as Hispanic or Latino.

Of the 51 patients dosed, 48 patients previously received on-demand bypassing agents before crossing over to marstacimab treatment and the data from these 48 patients were used for the primary efficacy analysis. This population was characterised by a severe bleeding phenotype. The mean ABRs for treated bleeds were 19.78 in the Observational Phase, prior to crossing over to weekly marstacimab prophylaxis. Of the 48 patients, 70.8% patients had one or more target joints at study entry and 25.0% had 3 or more target joints at study entry.

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

Table 4. Comparison of ABR with Hympavzi prophylaxis versus on-demand bypassing agent therapy in patients ≥ 12 years of age with factor VIII or factor IX inhibitors

Endpoints in the order of testing hierarchy	On-demand bypassing agent therapy during 6-month OP (N = 48)	Hympavzi prophylaxis during 12-month ATP (N = 48)
Treated bleeds (Primary)		
ABR, model-based (95% CI)	19.78 (16.12, 24.27)	1.39 (0.85, 2.29)
Ratio vs. OD (95% CI)	0.070 (0.042, 0.118)	
p-value	< 0.0001	
Participants with 0 bleeds, n (%)	1 (2.1)	26 (54.2)
Spontaneous bleeds, treated		
ABR, model-based (95% CI)	15.27 (12.07, 19.31)	0.87 (0.53, 1.43)
Ratio vs. OD (95% CI)	0.057 (0.035, 0.092)	
p-value	< 0.0001	
Joint bleeds, treated		
ABR, model-based (95% CI)	15.15 (11.87, 19.34)	1.10 (0.59, 2.04)
Ratio vs. OD (95% CI)	0.072 (0.038, 0.138)	
p-value	< 0.0001	
Total bleeds, treated and untreated		
ABR, model-based (95% CI)	27.29 (22.54, 33.03)	4.36 (2.65, 7.18)
Ratio vs. OD (95% CI)	0.160 (0.102, 0.249)	
p-value	< 0.0001	
Target joint bleeds, treated		
ABR, model-based (95% CI)	6.30 (4.32, 9.20)	0.79 (0.36, 1.74)
Ratio vs. OD (95% CI)	0.126 (0.062, 0.256)	
p-value	0.0001	

- 2-sided p-value for the null hypothesis that the ratio = 0.5.
- The estimated mean, ratio, and confidence intervals (CIs) for the ABR come from negative binomial regression model.
- Bleed definitions adapted based on ISTH criteria.
- Treated bleeds = bleeds treated with bypassing agent
- Total bleeds = bleeds treated and not treated with bypassing agent
- ABR = Annualised Bleeding Rate; CI = Confidence Interval; OD = On-Demand; OP = Observational Phase; ATP = Active Treatment Phase

Study B7841007 interim analysis (Inhibitor cohort)

In the OLE of the pivotal Phase 3 study, 47 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 41 months (mean 19 months) where marstacimab was shown to maintain long-term 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 5.

Table 5. ABR with Hympavzi prophylaxis over time in patients ≥ 12 years of age with factor VIII or factor IX inhibitors

Endpoint	Time interval during OLE Study B7841007*			
	Year 1 (N = 47)	**Year 2 (N = 32)**	**≥ Year 3 (N = 14)**	**Overall (N = 47)**
Treated bleeds				
Mean ABR (95% CI)	1.20 (0.72, 2.02)	1.16 (0.49, 2.76)	0.42 (0.16, 1.13)	1.19 (0.72, 1.95)
Median ABR (IQR)	0.00 (0.00, 2.00)	0.00 (0.00, 1.21)	0.00 (0.00, 0.94)	0.00 (0.00, 1.18)

*Patients received marstacimab for up to an additional 41 months (mean 19 months) during B7841007.
Year 1: Day 1 to Day 365; Year 2: Day 366 to Day 730; ≥ Year 3: Day 731 to the 41-month data cut-off

- 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 come from the descriptive summary.
- ABR = Annualised Bleeding Rate; CI = Confidence Interval; IQR = Interquartile Range; N = number of patients who contributed data for analyses at each time interval

Immunogenicity

Following at least 1 year of subcutaneous weekly marstacimab dosing in haemophilia patients with and without inhibitors in the pooled Studies B7841005/B7841007, 39 of the 167 (23.4%) anti-drug antibody (ADA)-evaluable marstacimab-treated patients developed ADAs. Incidences were 25.2% (34/135) in adults, 15.6% (5/32) in adolescents, 23.5% (12/51) in patients with inhibitors and 23.3% (27/116) in patients without inhibitors. ADAs were transient in 67% (26/39) and persistent in 31% (12/39) of the ADA-positive patients. ADA titres resolved in 38/39 (97%) patients by the end of the study. Neutralising antibodies (NAbs) developed in 8/167 (4.8%; 6/116 patients without inhibitors and 2/51 patients with inhibitors) ADA-evaluable marstacimab-treated patients during the study. The NAbs were transient in the majority (87.5%) of patients and no patients were NAb positive at the end of the study. Although slightly lower mean marstacimab concentrations (approximately 10%-36% 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 patients with ADAs (including NAbs) and those without.

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 with and without inhibitors as well as using a population pharmacokinetic analysis on a database composed of 287 participants (224 haemophilia patients with and without inhibitors 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 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.

No clinically meaningful differences were seen in marstacimab exposures between haemophilia participants with and without inhibitors.

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 $C_{max,ss}$, $C_{min,ss}$, and $C_{avg,ss}$ for adults and adolescents are shown in Table 6.

Table 6. Steady-state marstacimab plasma concentrations in haemophilia A and B patients with and without inhibitors following once-weekly subcutaneous administration of 150 mg marstacimab (with a loading dose of 300 mg subcutaneous)

Parameter	Adults without inhibitors	Adults with inhibitors	Adolescents without inhibitors	Adolescents with inhibitors
$C_{min,ss}$ (ng/mL)	13 200 (95.5%)	16 100 (77.9%)	30 100 (74.5%)	35 500 (69.0%)
$C_{max,ss}$ (ng/mL)	17 700 (79.6%)	21 900 (67.7%)	37 300 (65.9%)	44 700 (63.5%)
$C_{avg,ss}$ (ng/mL)	16 100 (84.3%)	19 800 (70.3%)	34 800 (68.7%)	41 400 (65.2%)

- 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 modelling. No clinically relevant differences were seen in marstacimab bioavailability between arm, thigh and abdomen.

Distribution

Marstacimab steady-state volume of distribution in haemophilia patients was 6.0 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 0.017 L/hr. Based on population pharmacokinetic analysis, 90% of marstacimab is expected to be eliminated by the end of

approximately 1 month after the last dose (median time for 50% of drug to be eliminated is approximately 7 to 11 days).

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 exposures (geometric mean steady state AUC, C_{max} and C_{min}) were 2.6 to 3.2-fold higher in adolescents compared to adult haemophilia patients; however body weight accounts for most of these differences in exposures. These differences 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 after adjusting for body weight. Marstacimab weight-adjusted linear clearance was 26% higher in Asian participants as compared to non-Asian participants. 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 = 198; eGFR ≥ 90 mL/min/1.73 m^2) or mild renal impairment (N = 25; 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 = 204; total bilirubin and AST ≤ ULN) or mild hepatic impairment (N = 20; 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.

Drug-drug interaction

Coadministration of marstacimab (50 mg/kg) with rFVIIa in haemostatically normal rats was tolerated at a dose of 0.8 mg/kg rFVIIa but at a higher dose of rFVIIa (3 mg/kg) was associated with an increased incidence and/or severity of acute thrombi/emboli in the lung and injection site. Coadministration of marstacimab (30 mg/kg) with aPCC (10-100 U/kg/day) in haemostatically normal rats resulted in higher mean thrombin-antithrombin complexes and mean platelet volume than were observed with aPCC alone.

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

Hympavzi 150 mg solution for injection in pre-filled syringe

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.

Hympavzi 150 mg solution for injection in pre-filled pen

Hympavzi 150 mg solution for injection in pre-filled pen is available in a pack containing 1 single-dose pre-filled pen and in multipacks containing 4 (4 packs of 1) single-dose pre-filled pens.

The syringe inside the pen is made from Type I glass with a plunger stopper (chlorobutyl elastomer) and a stainless steel 27 gauge, ½ inch staked needle with a needle shield (thermoplastic elastomer).

Each pre-filled pen contains 1 mL solution for injection.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Hympavzi 150 mg solution for injection in pre-filled syringe
EU/1/24/1874/001

Hympavzi 150 mg solution for injection in pre-filled pen
EU/1/24/1874/002 1 pre-filled pen
EU/1/24/1874/003 4 pre-filled pens

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 November 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Wyeth BioPharma
Division of Wyeth Pharmaceuticals LLC
One Burtt Road
Andover, MA 01810
USA

Name and address of the manufacturer responsible for batch release

Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs-Sint-Amands
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Hympavzi in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the Patient Card including communication media and distribution modalities, with the National Competent Authority.

  - The Patient Card is aimed at informing patients on the safe use of marstacimab and about the important risks associated with marstacimab. The Patient Card should be shared with the patient's healthcare professionals (HCPs) to inform the HCP of the patient's treatment with marstacimab and the risk of thromboembolic events.

The MAH shall ensure that in each Member State where Hympavzi is marketed, all HCPs and patients/carers who are expected to prescribe, use or oversee the administration of Hympavzi have access to/are provided with the Patient Card. The Patient Card will be translated in the local language to ensure understanding of proposed mitigation measures by HCPs and patients.

The Patient Card:

- Is to inform patients on the safe use of marstacimab and about the important risks associated with marstacimab.
- The patient should show the Patient Card to a doctor or a nurse whenever they have an appointment or go to the emergency room to seek care.
- Is to inform healthcare professionals that the patient is being treated with marstacimab.
- Reminds patients of the risk of thromboembolism during marstacimab treatment.
- Reminds the patient when and how they should seek medical advice for any symptoms suggestive of a thromboembolic event.
- Reminds patients when and how to report relevant signs and symptoms of thromboembolism.
- Provides contact details of the patient's marstacimab prescriber and emergency contacts.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Hympavzi 150 mg solution for injection in pre-filled syringe
marstacimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe contains 150 mg marstacimab in 1 mL solution.

3. LIST OF EXCIPIENTS

Disodium edetate, L-Histidine, L-Histidine monohydrochloride, Polysorbate 80, Sucrose, Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe
1 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Do not shake.
Read the package leaflet before use.

Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1874/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hympavzi 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Hympavzi 150 mg solution for injection
marstacimab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

Store in a refrigerator.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (SINGLE PACK)

1. NAME OF THE MEDICINAL PRODUCT

Hympavzi 150 mg solution for injection in pre-filled pen
marstacimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen contains 150 mg marstacimab in 1 mL solution.

3. LIST OF EXCIPIENTS

Disodium edetate, L-Histidine, L-Histidine monohydrochloride, Polysorbate 80, Sucrose, Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen
1 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Do not shake.
Read the package leaflet before use.

Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1874/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hympavzi 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Hympavzi 150 mg solution for injection in pre-filled pen
marstacimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 150 mg marstacimab in 1 mL solution.

3. LIST OF EXCIPIENTS

Disodium edetate, L-Histidine, L-Histidine monohydrochloride, Polysorbate 80, Sucrose, Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
Multipack: 4 (4 packs of 1) 1 mL pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Do not shake.
Read the package leaflet before use.

Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1874/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hympavzi 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON FOR MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Hympavzi 150 mg solution for injection in pre-filled pen
marstacimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen contains 150 mg marstacimab in 1 mL solution.

3. LIST OF EXCIPIENTS

Disodium edetate, L-Histidine, L-Histidine monohydrochloride, Polysorbate 80, Sucrose, Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen
1 mL
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Do not shake.
Read the package leaflet before use.

Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1874/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hympavzi 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Hympavzi 150 mg solution for injection
marstacimab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

Store in a refrigerator.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Hympavzi 150 mg solution for injection in pre-filled syringe
marstacimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or the child in your care only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Hympavzi is and what it is used for
2. What you need to know before you use Hympavzi
3. How to use Hympavzi
4. Possible side effects
5. How to store Hympavzi
6. Contents of the pack and other information

1. What Hympavzi is and what it is used for

Hympavzi contains the active substance marstacimab. Marstacimab is a monoclonal antibody, a type of protein designed to recognise and attach to a specific target in the body called tissue factor pathway inhibitor (TFPI).

Hympavzi is a medicine used to prevent or reduce bleeding in patients 12 years of age and older, weighing at least 35 kg, with:

- Haemophilia A (congenital factor VIII deficiency)
  - who have not developed factor VIII inhibitors with severe disease (the factor VIII blood level is less than 1%), or
  - who have developed factor VIII inhibitors
- Haemophilia B (congenital factor IX deficiency)
  - who have not developed factor IX inhibitors with severe disease (the factor IX blood level is less than 1%), or
  - who have developed factor IX inhibitors.

Haemophilia A is an inherited bleeding disorder caused by a lack of factor VIII. Haemophilia B is an inherited bleeding disorder caused by lack of factor IX. Factor VIII and factor IX are proteins required for blood to clot and stop any bleeding. Some patients with haemophilia can develop factor VIII or factor IX inhibitors (antibodies in the blood that act against replacement factor VIII or factor IX medicines and prevent them from working properly).

The active substance in Hympavzi, marstacimab, recognises and attaches to TFPI, a protein that prevents blood from clotting too much. By attaching to TFPI, marstacimab decreases how well it works, which promotes the formation of thrombin (a protein that plays a crucial role in blood clotting when there is an injury or damage to the body). This helps to increase clotting and stop bleeding in patients with haemophilia.

2. What you need to know before you use Hympavzi

Do not use Hympavzi
- if you are allergic to marstacimab or any of the other ingredients of this medicine (listed in section 6). If you are not sure if you are allergic, talk to your doctor, pharmacist or nurse before using Hympavzi.

Warnings and precautions
Talk to your doctor before using Hympavzi.

Before you start using Hympavzi, it is very important to talk to your doctor about using other factor VIII and factor IX products or "bypassing agents" (products that help blood clot but work in a different way from Hympavzi) while using Hympavzi. **This is because treatment with factor VIII and factor IX products or bypassing agents may need to change while receiving Hympavzi.** Examples of bypassing agents include activated prothrombin complex concentrate (aPCC) and recombinant FVIIa (rFVIIa). You may need to use other factor VIII or factor IX products or bypassing agents to treat episodes of breakthrough bleeding while using Hympavzi. Carefully follow your healthcare provider's instructions regarding when and how to use these products while using Hympavzi.

Blood clots (thromboembolic events)
Hympavzi increases how easily your blood clots and may cause blood clots in the blood vessels (so called thromboembolic events). Blood clots may be life-threatening. Tell your doctor if you have a history of blood clots or if you have a condition which increases your risk of blood clots. This includes if you:

- have a history of coronary artery disease (heart disease caused by narrowing or blockage of blood vessels supplying the heart muscle)
- have a history of ischaemic disease (reduced blood flow due to narrowed or blocked blood vessels)
- have a history of blood clots in veins or arteries
- have a genetic condition that increases your risk for blood clotting (such as Factor V Leiden)
- are bedridden, immobilised or off your feet for a long time
- are obese (overweight)
- are a smoker
- currently have serious infections
- currently have sepsis (blood poisoning)
- currently have trauma or crush injuries
- currently have cancer
- are having a surgery

Stop using Hympavzi, and talk to a doctor immediately if you notice any symptoms of a possible blood clot including the following side effects:

- swelling or pain in arms or legs
- redness or discolouration in your arms or legs
- shortness of breath
- pain in chest or upper back
- fast heart rate
- coughing up blood
- feeling faint
- headache
- numbness in your face
- eye pain or swelling
- trouble seeing

Allergic reactions
Symptoms of allergic reaction have been seen in people using Hympavzi. Stop using Hympavzi and get medical help right away if you get any symptoms of a possible severe allergic reaction including the following:

- rash, hives, generalised itching
- swelling of the face, lips, tongue or throat
- difficulty breathing or swallowing
- dizziness

Children below the age of 12 years
Hympavzi should not be used in children less than 1 year of age, and is not recommended for individuals below 12 years of age. The safety and benefits of this medicine are not yet known in this population.

Other medicines and Hympavzi
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy, contraception and breast-feeding
If you are able to get pregnant, you should use an effective method of contraception (birth control) during treatment with Hympavzi and for at least 1 month after the last injection.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Your doctor will consider the benefit of you using Hympavzi against the risk to your unborn baby.

If you are breast-feeding, ask your doctor for advice on whether to stop breast-feeding or stop using Hympavzi. Your doctor will consider the benefit of you using Hympavzi against the benefits for your nursing infant.

Driving and using machines
Hympavzi has no or limited effect on the ability to drive or use machines.

Hympavzi contains polysorbate 80
This medicine contains 0.2 mg of polysorbate 80 in each mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

Hympavzi contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 1 mL, that is to say essentially ‘sodium-free’.

3. How to use Hympavzi

Your treatment will be started under the supervision of a doctor qualified to care for patients with haemophilia. Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your healthcare provider will provide instructions for stopping your current treatment when switching from factor- or non-factor-based medicines or bypassing agents to Hympavzi. Contact your healthcare provider if you are not sure what to do.

If you are severely ill or need to undergo major surgery, tell your healthcare provider that you are using Hympavzi.

Keeping a record
Each time you use Hympavzi, record the name and batch number of the medicine.

How Hympavzi is given
- Hympavzi is given as an injection under the skin (subcutaneous injection). Do not inject it into a vein or muscle.
- For a more comfortable injection, Hympavzi may be allowed to warm at room temperature in the carton away from direct sunlight for about 15 to 30 minutes prior to use. Hympavzi should not be warmed in any other way. For example, do not warm in hot water or a microwave.

Before you use the syringe for the first time, your doctor, nurse or pharmacist will show you and/or your caregiver how to inject Hympavzi. **If you inject Hympavzi yourself or if your caregiver injects it, you or your caregiver must carefully read and follow the detailed instructions for use on the reverse side of this leaflet.**

Where to inject Hympavzi
- Your doctor or nurse will show you and/or your caregiver which areas of the body should be injected with Hympavzi. The best place to give Hympavzi is the belly area (abdomen) or thigh. Injections to the upper arm should be given by a caregiver, doctor, nurse or pharmacist only.
- Change the site of injection on your body each time an injection is given.
- If more than one injection is required to deliver a complete dose, each injection should be given at a different injection site.
- If you are using other medicines that must be injected under the skin, these injections should be given at a different injection site.

How much Hympavzi to use
Your treatment will start with a loading dose which will then be followed by a maintenance dose given every week:
- Loading dose (a higher starting dose to quickly build up levels in the body): The recommended dose is 300 mg.
- Maintenance dose: The recommended dose is 150 mg.

You should use this medicine once a week (any time of day) on the same day each week.

You should record which day of the week you use Hympavzi to help you remember to inject this medicine once a week.

Depending on how you respond to Hympavzi, your doctor may change your maintenance dose as needed, up to a maximum of 300 mg weekly.

Use in adolescents
Hympavzi can be used in adolescents 12 years of age and older. An adolescent can self-inject the medicine provided the adolescent's doctor or nurse and the parent or caregiver agree and the patient is trained to do so.

If you use more Hympavzi than you should
If you have used more Hympavzi than you are supposed to, tell your doctor immediately. You may be at risk of developing side effects such as blood clots and require medical attention. Always use Hympavzi exactly as your doctor has told you, and check with your doctor, pharmacist or nurse if you are not sure.

If you forget to use Hympavzi
- If you forget your scheduled dose, inject the forgotten dose as soon as possible before the day of the next scheduled dose. Then continue to inject the medicine as scheduled. Do not inject a double dose to make up for a forgotten dose.
- If you forget two scheduled doses in a row (that is if it has been more than 13 days since your last injection), contact your doctor as soon as possible and ask what to do.
- If you are not sure what to do, ask your doctor, pharmacist or nurse.

If you stop using Hympavzi
Do not stop using Hympavzi without talking to your doctor. If you stop using Hympavzi, you may no longer be protected against bleeding.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Hympavzi may cause a rash (seen in up to 1 in 10 people), which may be severe. Contact your doctor immediately if you have a severe rash; some rashes may be serious. Do not use Hympavzi again until you have talked with your doctor about your rash.

Hympavzi may cause blood clots (thromboembolism) (seen in up to 1 in 100 people). Stop using Hympavzi and contact your doctor immediately if you notice any signs or symptoms of a possible blood clot. Please refer to section 2 "What you need to know before you use Hympavzi" for a list of possible symptoms of a blood clot (thromboembolic event).

Other side effects
Tell your doctor, nurse or pharmacist if you get any of these side effects.

Very common (may affect more than 1 in 10 people)
- a reaction in the area where the injection is given (including itching, swelling, redness, pain, bruising, bleeding, hardening)

Common (may affect up to 1 in 10 people)
- headache
- high blood pressure
- itching (pruritus)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Hympavzi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled syringe label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C - 8 °C). Do not freeze.

Keep the pre-filled syringe in the original carton in order to protect from light.

Hympavzi may be removed from the refrigerator and stored in its original carton for up to 7 days at room temperature (up to 30 °C). Do not return Hympavzi to the refrigerator after storing at room temperature. If Hympavzi has been at room temperature for more than 7 days, throw it away, even if it contains unused medicine.

Do not shake.

Remove Hympavzi from the refrigerator prior to use. For a more comfortable injection, Hympavzi may be allowed to warm at room temperature in the carton for about 15 to 30 minutes away from direct sunlight prior to use.

Before using the medicine, check the solution for particles or discolouration. Do not use if you notice that the medicine is cloudy, dark yellow, or contains flakes or particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Hympavzi contains
- The active substance is marstacimab.
- The other ingredients are disodium edetate, L-histidine, L-histidine monohydrochloride, polysorbate 80 (E 433), sucrose, water for injections (see section 2 “Hympavzi contains polysorbate 80” and “Hympavzi contains sodium”).

What Hympavzi looks like and contents of the pack
Hympavzi is a clear and colourless to light yellow solution for injection (injection) in a pre-filled syringe.
Each pack of Hympavzi contains 1 pre-filled syringe.

Marketing Authorisation Holder
Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

Manufacturer
Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs-Sint-Amands
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Luxembourg/Luxemburg
Pfizer NV/SA
Tél/Tel: +32 (0)2 554 62 11

България
Пфайзер Люксембург САРЛ, Клон България
Тел.: +359 2 970 4333

Česká republika
Pfizer, spol. s r.o.
Tel: +420 283 004 111

Danmark
Pfizer ApS
Tlf.: +45 44 20 11 00

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje
Tel: +370 5 251 4000

Magyarország
Pfizer Kft.
Tel.: + 36 1 488 37 00

Malta
Vivian Corporation Ltd.
Tel: +356 21344610

Nederland
Pfizer bv
Tel: +31 (0)800 63 34 636

Deutschland
PFIZER PHARMA GmbH
Tel: +49 (0)30 550055-51000

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel: +372 666 7500

Ελλάδα
Pfizer Ελλάς A.E.
Τηλ: +30 210 6785800

España
Pfizer, S.L.
Tel: +34 91 490 99 00

France
Pfizer
Tél: +33 (0)1 58 07 34 40

Hrvatska
Pfizer Croatia d.o.o.
Tel: +385 1 3908 777

Ireland
Pfizer Healthcare Ireland Unlimited Company
Tel: +1800 633 363 (toll free)
Tel: +44 (0)1304 616161

Ísland
Icepharma hf.
Sími: +354 540 8000

Italia
Pfizer S.r.l.
Tel: +39 06 33 18 21

Κύπρος
Pfizer Ελλάς A.E. (Cyprus Branch)
Τηλ: +357 22817690

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
Tel: + 371 670 35 775

Norge
Pfizer AS
Tlf: +47 67 52 61 00

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp. z o.o.
Tel.: +48 22 335 61 00

Portugal
Laboratórios Pfizer, Lda.
Tel: +351 21 423 5500

România
Pfizer Romania S.R.L.
Tel: +40 (0) 21 207 28 00

Slovenija
Pfizer Luxembourg SARL
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Tel: +386 (0)1 52 11 400

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: + 421 2 3355 5500

Suomi/Finland
Pfizer Oy
Puh/Tel: +358 (0)9 430 040

Sverige
Pfizer AB
Tel: +46 (0)8 550 520 00

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

INSTRUCTIONS FOR USE
Hympavzi 150 mg solution for injection in pre-filled syringe

This 'Instructions for Use' contains information on how to inject Hympavzi.

Read this 'Instructions for Use' carefully before using Hympavzi pre-filled syringe and each time you get a refill prescription as there may be new information.

Your doctor, nurse or pharmacist should show you or your caregiver how to prepare and inject a dose of Hympavzi the right way before you use it for the first time.

Do not inject yourself or someone else until you have been shown how to inject Hympavzi.

Important Information

- Each Hympavzi pre-filled syringe is a single-dose pre-filled syringe (called "syringe" in this 'Instructions for Use'). The Hympavzi pre-filled syringe contains 150 mg of Hympavzi for injection under the skin (subcutaneously).
- **Do not** inject Hympavzi into a vein or muscle.
- **Do not** shake Hympavzi.
- To help you remember when to inject Hympavzi, you can mark your calendar ahead of time. Call your doctor, nurse or pharmacist if you or your caregiver have any questions about the right way to inject Hympavzi.

How To Store Hympavzi

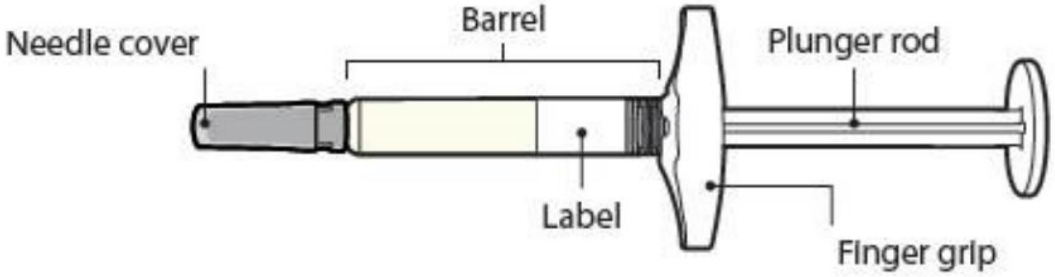
- Store unused Hympavzi in the refrigerator between 2 °C to 8 °C. Do not freeze Hympavzi. Store Hympavzi in its original carton to protect from direct light.
- If necessary, Hympavzi may be stored in its original carton at room temperature up to 30 °C for up to 7 days. **Do not** use Hympavzi if it has been out of the refrigerator for longer than 7 days. Throw away (dispose of) any Hympavzi that has been kept at room temperature for longer than 7 days.
- **Do not** use past the expiry date printed on the Hympavzi pre-filled syringe.
- **Keep Hympavzi and all other medicines out of the reach of children.**

Supplies Needed For Hympavzi Injection

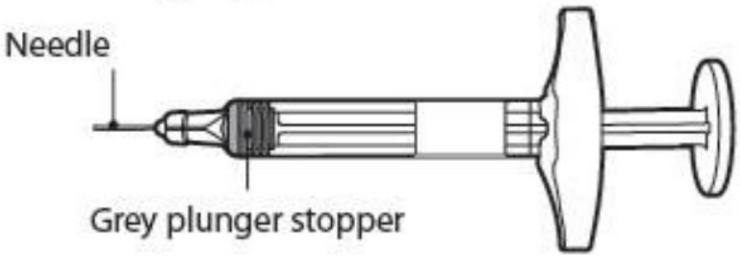
Gather the following supplies on a clean flat surface:
- 1 Hympavzi pre-filled syringe.
- 1 alcohol swab (not included).
- 1 cotton ball or gauze pad (not included).
- 1 sharps disposal container for syringe disposal (not included).

Always hold Hympavzi pre-filled syringe by the barrel to prevent damage.

Hympavzi pre-filled syringe BEFORE use:



Hympavzi pre-filled syringe AFTER use:



Preparation Steps

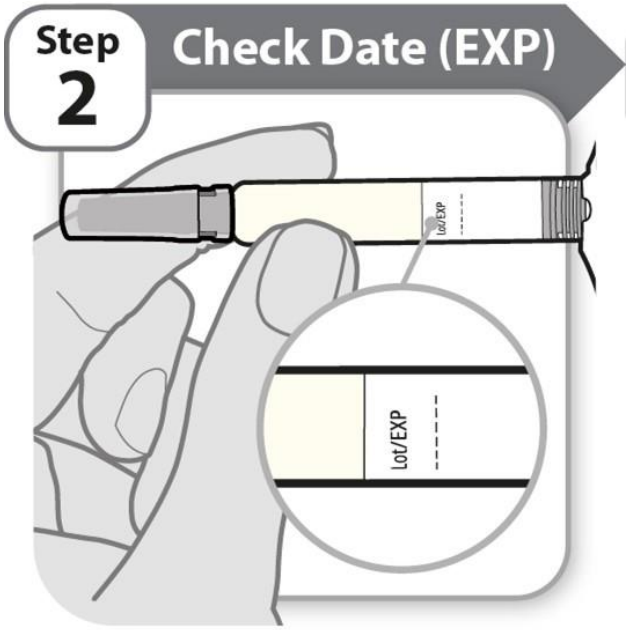
Step 1 – Getting Ready

- **Remove** the syringe from its carton and keep out of direct sunlight.
- **Make sure** the name Hympavzi appears on the carton and syringe label.
- **Check the syringe** for any visible damage such as cracks or leaks.
- **Wash and dry** your hands.
- **Do not remove the needle cover until you are ready to inject.**
- **Throw away (dispose of)** the syringe if it is damaged, or if the syringe or the carton containing the syringe has been dropped.
- **Do not** use the syringe if:
  - it has been stored in direct light. Exposure to room light during dose preparation and injection is acceptable.
  - it has been frozen or thawed or it has been out of the refrigerator for more than 7 days.
- **Do not** shake the syringe. Shaking can damage Hympavzi.

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

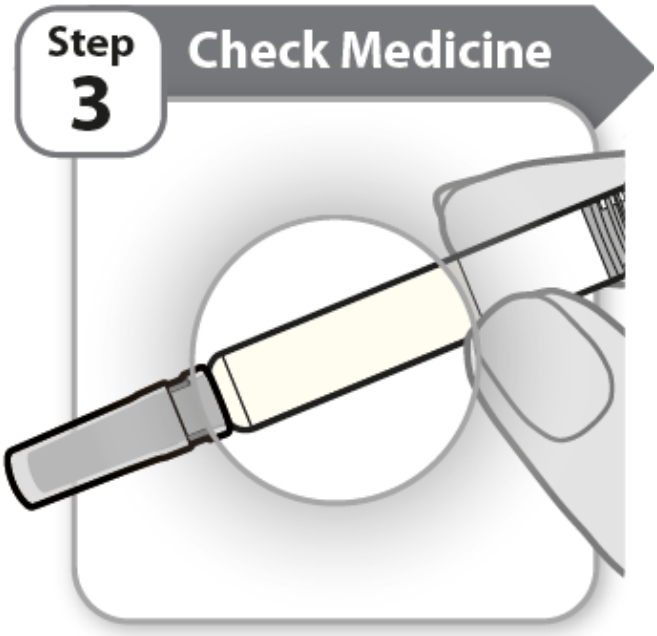
Do not use any other methods to warm up the syringe, such as warming the syringe in a microwave or hot water.

Step 2 – Check Date (EXP)



- **Check** the expiry date (EXP) printed on the syringe label.
- **Do not** use if the expiry date has passed.

Step 3 – Check Medicine

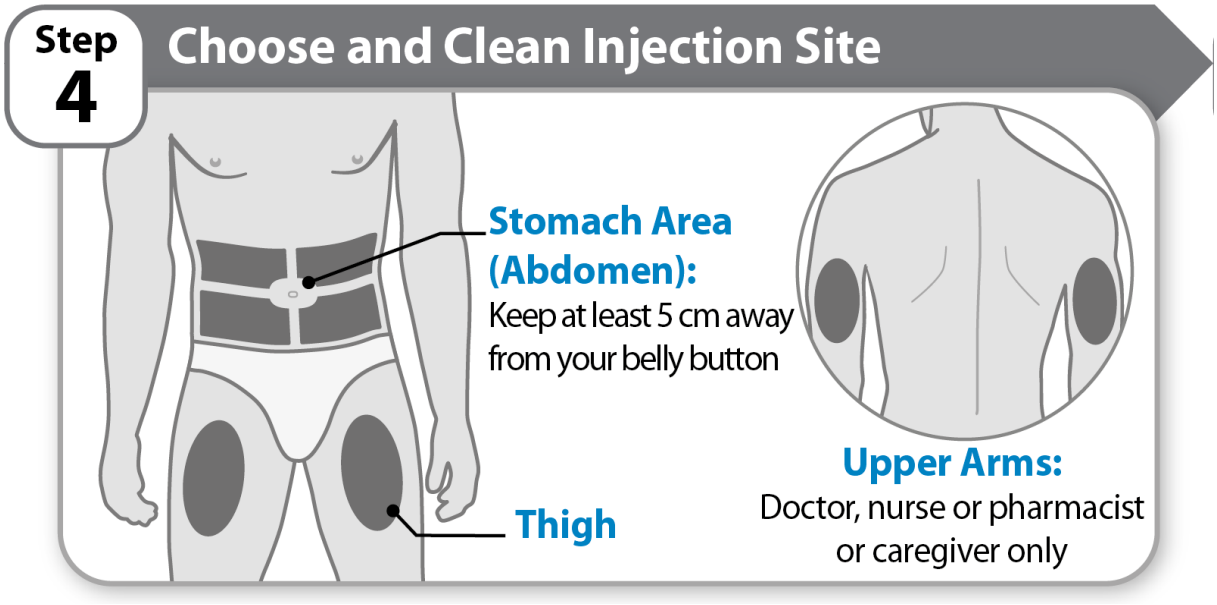


- **Gently** tilt the syringe back and forth.
- **Look** carefully at the medicine in the syringe.
  - The medicine should be clear and colourless to light yellow.
  - **Do not** use the syringe if the medicine is cloudy, dark yellow, or contains flakes or particles.

Note: It is normal to see air bubble(s).

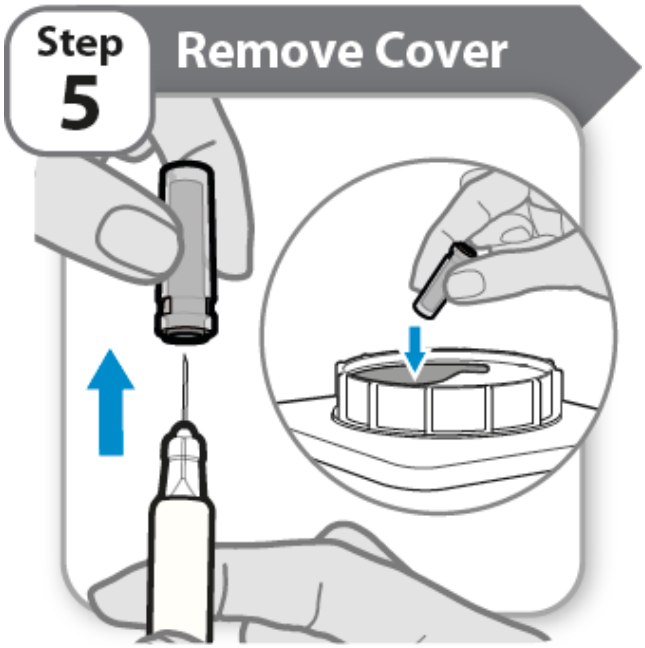
If you have any questions about the medicine, contact your doctor, nurse or pharmacist.

Step 4 – Choose and Clean Injection Site



- **Choose** an injection site on your stomach area (abdomen) or thigh unless a different site has been suggested by your doctor, nurse or pharmacist. Hympavzi may also be injected into your upper arms by a doctor, nurse, pharmacist or caregiver only. Keep at least 5 cm away from your belly button.
- **Change** the injection site each time you give yourself an injection of Hympavzi. You may use the same area of your body, but be sure to choose a different injection site in that area.
- **Clean** the injection site with soap and water, or an alcohol swab if convenient.
- **Allow** the site to dry. **Do not** touch, fan or blow on the cleaned injection site.
- **Do not** inject Hympavzi into bony areas or areas on your skin that are bruised, red, sore (tender) or hard. Avoid injecting into areas with scars or stretch marks.
- **Do not** inject Hympavzi into a vein or muscle.
- **Do not** inject Hympavzi through your clothes.

Step 5 – Remove Cover



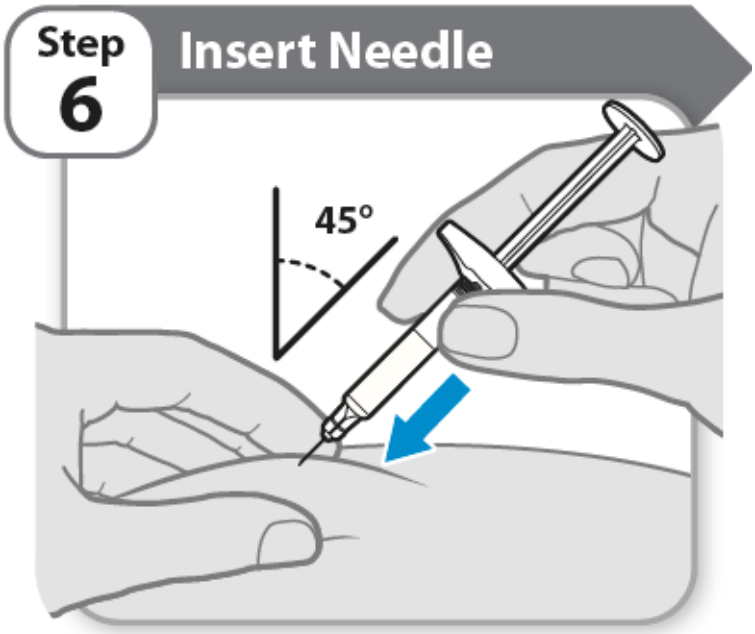
- **Hold** the syringe by the barrel.
- **Pull** the needle cover straight off carefully.
- **Put** the needle cover into a sharps disposal container right away. You will not need it again.
- **Do not** touch the needle or let it touch any surfaces.

Note: It is normal to see a few drops of medicine at the needle tip.

Caution: Handle the syringe with care to avoid an accidental needle injury.

Injection Steps

Step 6 – Insert Needle

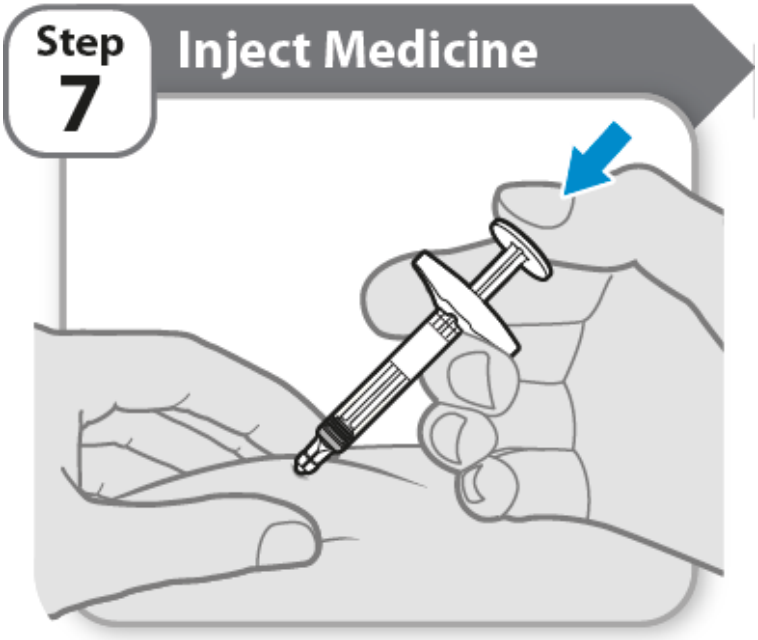


- **Pinch** your skin between your thumb and fingers to create a firm surface.
- **Insert** the needle to its full depth into your skin, at a 45° angle, as shown.

Keep your skin pinched throughout the injection.

Caution: If you change your mind where to inject after inserting the needle into your skin, you will need to throw away (dispose of) the syringe and get a new Hympavzi pre-filled syringe.

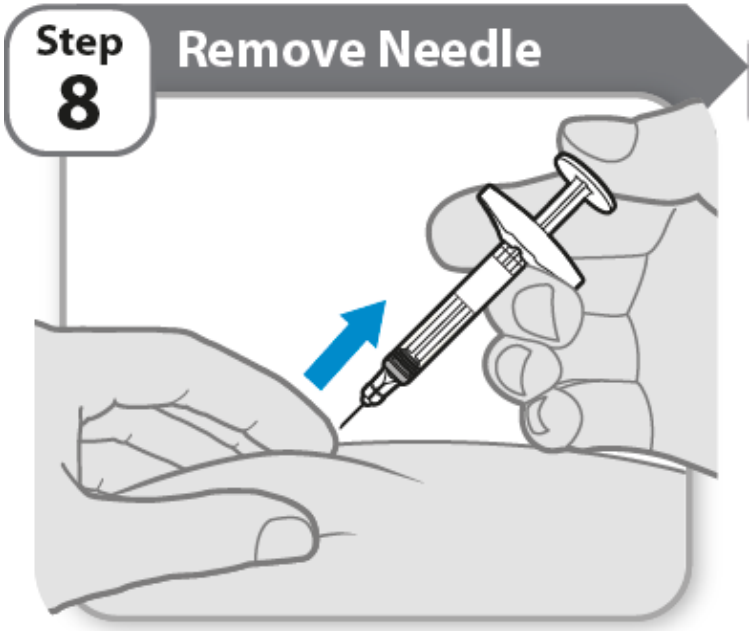
Step 7 – Inject Medicine



- **Push** the plunger rod all the way down using slow and constant pressure, until the barrel is empty.

Note: It is recommended to count to 5 slowly after the plunger rod has been fully pushed down before removing the needle from your skin.

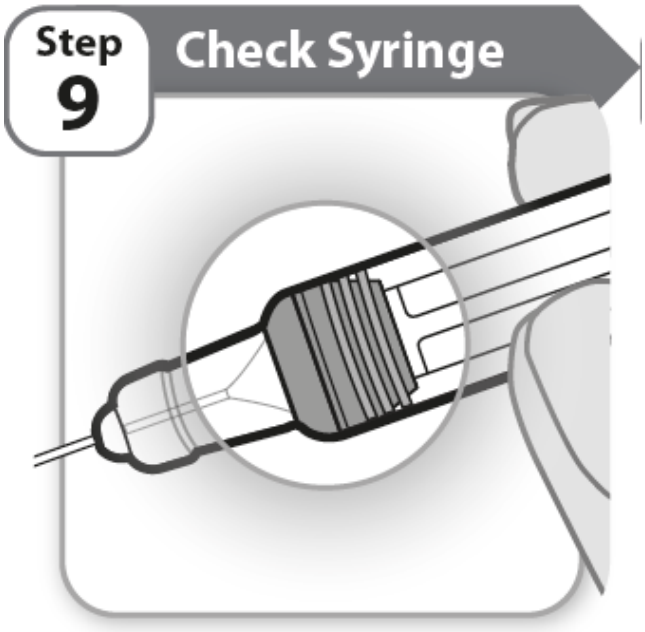
Step 8 – Remove Needle



- **Pull** the needle out of your skin at the same angle at which it entered.

Note: If you see a small drop of medicine on your skin, wait a little longer before removing the needle when you give your next injection.

Step 9 – Check Syringe



- **Check** the syringe to make sure the grey plunger stopper is in the position shown.

If the grey plunger stopper is not in the position shown, this means you have not received a full dose. Call your doctor, nurse or pharmacist for help.

Never re-insert the needle.

Do not inject another dose.

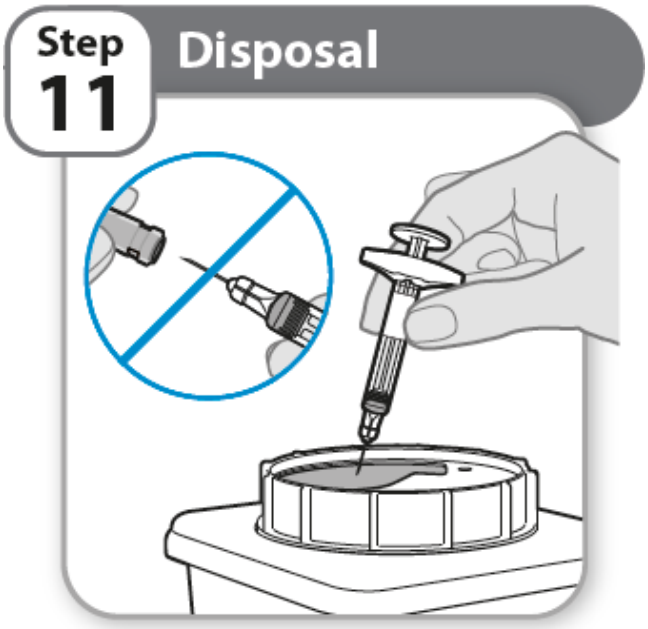
Step 10 – After Care



- **Press** lightly on the injection site for a few seconds with a clean cotton ball or gauze pad if you see a drop of blood.
- **Do not** rub the area.

Note: If bleeding does not stop, please contact your doctor, nurse or pharmacist.

Step 11 – Disposal



- **Put** the used syringe in a sharps disposal container as instructed by your doctor, nurse or pharmacist and in accordance with local health and safety laws.

Never re-cap the needle.

- **Do not** throw away (dispose of) syringes in the household waste.

Package leaflet: Information for the patient

Hympavzi 150 mg solution for injection in pre-filled pen
marstacimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or the child in your care only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Hympavzi is and what it is used for
2. What you need to know before you use Hympavzi
3. How to use Hympavzi
4. Possible side effects
5. How to store Hympavzi
6. Contents of the pack and other information

1. What Hympavzi is and what it is used for

Hympavzi contains the active substance marstacimab. Marstacimab is a monoclonal antibody, a type of protein designed to recognise and attach to a specific target in the body called tissue factor pathway inhibitor (TFPI).

Hympavzi is a medicine used to prevent or reduce bleeding in patients 12 years of age and older, weighing at least 35 kg, with:

- Haemophilia A (congenital factor VIII deficiency)
  - who have not developed factor VIII inhibitors with severe disease (the factor VIII blood level is less than 1%), or
  - who have developed factor VIII inhibitors
- Haemophilia B (congenital factor IX deficiency)
  - who have not developed factor IX inhibitors with severe disease (the factor IX blood level is less than 1%), or
  - who have developed factor IX inhibitors.

Haemophilia A is an inherited bleeding disorder caused by a lack of factor VIII. Haemophilia B is an inherited bleeding disorder caused by lack of factor IX. Factor VIII and factor IX are proteins required for blood to clot and stop any bleeding. Some patients with haemophilia can develop factor VIII or factor IX inhibitors (antibodies in the blood that act against replacement factor VIII or factor IX medicines and prevent them from working properly).

The active substance in Hympavzi, marstacimab, recognises and attaches to TFPI, a protein that prevents blood from clotting too much. By attaching to TFPI, marstacimab decreases how well it works, which promotes the formation of thrombin (a protein that plays a crucial role in blood clotting when there is an injury or damage to the body). This helps to increase clotting and stop bleeding in patients with haemophilia.

2. What you need to know before you use Hympavzi

Do not use Hympavzi
- if you are allergic to marstacimab or any of the other ingredients of this medicine (listed in section 6). If you are not sure if you are allergic, talk to your doctor, pharmacist or nurse before using Hympavzi.

Warnings and precautions
Talk to your doctor before using Hympavzi.

Before you start using Hympavzi, it is very important to talk to your doctor about using other factor VIII and factor IX products or "bypassing agents" (products that help blood clot but work in a different way from Hympavzi) while using Hympavzi. **This is because treatment with factor VIII and factor IX products or bypassing agents may need to change while receiving Hympavzi.** Examples of bypassing agents include activated prothrombin complex concentrate (aPCC) and recombinant FVIIa (rFVIIa). You may need to use other factor VIII or factor IX products or bypassing agents to treat episodes of breakthrough bleeding while using Hympavzi. Carefully follow your healthcare provider's instructions regarding when and how to use these products while using Hympavzi.

Blood clots (thromboembolic events)
Hympavzi increases how easily your blood clots and may cause blood clots in the blood vessels (so called thromboembolic events). Blood clots may be life-threatening. Tell your doctor if you have a history of blood clots or if you have a condition which increases your risk of blood clots. This includes if you:

- have a history of coronary artery disease (heart disease caused by narrowing or blockage of blood vessels supplying the heart muscle)
- have a history of ischaemic disease (reduced blood flow due to narrowed or blocked blood vessels)
- have a history of blood clots in veins or arteries
- have a genetic condition that increases your risk for blood clotting (such as Factor V Leiden)
- are bedridden, immobilised or off your feet for a long time
- are obese (overweight)
- are a smoker
- currently have serious infections
- currently have sepsis (blood poisoning)
- currently have trauma or crush injuries
- currently have cancer
- are having a surgery

Stop using Hympavzi, and talk to a doctor immediately if you notice any symptoms of a possible blood clot including the following side effects:

- swelling or pain in arms or legs
- redness or discolouration in your arms or legs
- shortness of breath
- pain in chest or upper back
- fast heart rate
- coughing up blood
- feeling faint
- headache
- numbness in your face
- eye pain or swelling
- trouble seeing

Allergic reactions
Symptoms of allergic reaction have been seen in people using Hympavzi. Stop using Hympavzi and get medical help right away if you get any symptoms of a possible severe allergic reaction including the following:

- rash, hives, generalised itching
- swelling of the face, lips, tongue or throat
- difficulty breathing or swallowing
- dizziness

Children below the age of 12 years
Hympavzi should not be used in children less than 1 year of age, and is not recommended for individuals below 12 years of age. The safety and benefits of this medicine are not yet known in this population.

Other medicines and Hympavzi
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy, contraception and breast-feeding
If you are able to get pregnant, you should use an effective method of contraception (birth control) during treatment with Hympavzi and for at least 1 month after the last injection.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Your doctor will consider the benefit of you using Hympavzi against the risk to your unborn baby.

If you are breast-feeding, ask your doctor for advice on whether to stop breast-feeding or stop using Hympavzi. Your doctor will consider the benefit of you using Hympavzi against the benefits for your nursing infant.

Driving and using machines
Hympavzi has no or limited effect on the ability to drive or use machines.

Hympavzi contains polysorbate 80
This medicine contains 0.2 mg of polysorbate 80 in each mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

Hympavzi contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 1 mL, that is to say essentially ‘sodium-free’.

3. How to use Hympavzi

Your treatment will be started under the supervision of a doctor qualified to care for patients with haemophilia. Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your healthcare provider will provide instructions for stopping your current treatment when switching from factor- or non-factor-based medicines or bypassing agents to Hympavzi. Contact your healthcare provider if you are not sure what to do.

If you are severely ill or need to undergo major surgery, tell your healthcare provider that you are using Hympavzi.

Keeping a record
Each time you use Hympavzi, record the name and batch number of the medicine.

How Hympavzi is given
- Hympavzi is given as an injection under the skin (subcutaneous injection). Do not inject it into a vein or muscle.
- For a more comfortable injection, Hympavzi may be allowed to warm at room temperature in the carton away from direct sunlight for about 15 to 30 minutes prior to use. Hympavzi should not be warmed in any other way. For example, do not warm in hot water or a microwave.

Before you use the pen for the first time, your doctor, nurse or pharmacist will show you and/or your caregiver how to inject Hympavzi. **If you inject Hympavzi yourself or if your caregiver injects it, you or your caregiver must carefully read and follow the detailed instructions for use on the reverse side of this leaflet.**

Where to inject Hympavzi
- Your doctor or nurse will show you and/or your caregiver which areas of the body should be injected with Hympavzi. The best place to give Hympavzi is the belly area (abdomen) or thigh. Injections to the buttocks should be given by a caregiver, doctor, nurse or pharmacist only.
- Change the site of injection on your body each time an injection is given.
- If more than one injection is required to deliver a complete dose, each injection should be given at a different injection site.
- If you are using other medicines that must be injected under the skin, these injections should be given at a different injection site.

How much Hympavzi to use
Your treatment will start with a loading dose which will then be followed by a maintenance dose given every week:
- Loading dose (a higher starting dose to quickly build up levels in the body): The recommended dose is 300 mg.
- Maintenance dose: The recommended dose is 150 mg.

You should use this medicine once a week (any time of day) on the same day each week.

You should record which day of the week you use Hympavzi to help you remember to inject this medicine once a week.

Depending on how you respond to Hympavzi, your doctor may change your maintenance dose as needed, up to a maximum of 300 mg weekly.

Use in adolescents
Hympavzi can be used in adolescents 12 years of age and older. An adolescent can self-inject the medicine provided the adolescent's doctor or nurse and the parent or caregiver agree and the patient is trained to do so.

If you use more Hympavzi than you should
If you have used more Hympavzi than you are supposed to, tell your doctor immediately. You may be at risk of developing side effects such as blood clots and require medical attention. Always use Hympavzi exactly as your doctor has told you, and check with your doctor, pharmacist or nurse if you are not sure.

If you forget to use Hympavzi
- If you forget your scheduled dose, inject the forgotten dose as soon as possible before the day of the next scheduled dose. Then continue to inject the medicine as scheduled. Do not inject a double dose to make up for a forgotten dose.
- If you forget two scheduled doses in a row (that is if it has been more than 13 days since your last injection), contact your doctor as soon as possible and ask what to do.
- If you are not sure what to do, ask your doctor, pharmacist or nurse.

If you stop using Hympavzi
Do not stop using Hympavzi without talking to your doctor. If you stop using Hympavzi, you may no longer be protected against bleeding.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Hympavzi may cause a rash (seen in up to 1 in 10 people), which may be severe. Contact your doctor immediately if you have a severe rash; some rashes may be serious. Do not use Hympavzi again until you have talked with your doctor about your rash.

Hympavzi may cause blood clots (thromboembolism) (seen in up to 1 in 100 people). Stop using Hympavzi and contact your doctor immediately if you notice any signs or symptoms of a possible blood clot. Please refer to section 2 "What you need to know before you use Hympavzi" for a list of possible symptoms of a blood clot (thromboembolic event).

Other side effects
Tell your doctor, nurse or pharmacist if you get any of these side effects.

Very common (may affect more than 1 in 10 people)
- a reaction in the area where the injection is given (including itching, swelling, redness, pain, bruising, bleeding, hardening)

Common (may affect up to 1 in 10 people)
- headache
- high blood pressure
- itching (pruritus)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Hympavzi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled pen label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C - 8 °C). Do not freeze.

Keep the pre-filled pen in the original carton in order to protect from light.

Hympavzi may be removed from the refrigerator and stored in its original carton for up to 7 days at room temperature (up to 30 °C). Do not return Hympavzi to the refrigerator after storing at room temperature. If Hympavzi has been at room temperature for more than 7 days, throw it away, even if it contains unused medicine.

Do not shake.

Remove Hympavzi from the refrigerator prior to use. For a more comfortable injection, Hympavzi may be allowed to warm at room temperature in the carton for about 15 to 30 minutes away from direct sunlight prior to use.

Before using the medicine, check the solution for particles or discolouration. Do not use if you notice that the medicine is cloudy, dark yellow, or contains flakes or particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Hympavzi contains
- The active substance is marstacimab.
- The other ingredients are disodium edetate, L-histidine, L-histidine monohydrochloride, polysorbate 80 (E 433), sucrose, water for injections (see section 2 “Hympavzi contains polysorbate 80” and “Hympavzi contains sodium”).

What Hympavzi looks like and contents of the pack
Hympavzi is a clear and colourless to light yellow solution for injection (injection) in a pre-filled pen. Hympavzi 150 mg solution for injection in pre-filled pen is available in a pack containing 1 pre-filled pen and in multipacks containing 4 (4 packs of 1) pre-filled pens.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

Manufacturer
Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs-Sint-Amands
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Luxembourg/Luxemburg
Pfizer NV/SA
Tél/Tel: +32 (0)2 554 62 11

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje
Tel: +370 5 251 4000

България
Пфайзер Люксембург САРЛ, Клон България
Тел.: +359 2 970 4333

Magyarország
Pfizer Kft.
Tel.: + 36 1 488 37 00

Česká republika
Pfizer, spol. s r.o.
Tel: +420 283 004 111

Malta
Vivian Corporation Ltd.
Tel: +356 21344610

Danmark
Pfizer ApS
Tlf.: +45 44 20 11 00

Deutschland
PFIZER PHARMA GmbH
Tel: +49 (0)30 550055-51000

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel: +372 666 7500

Ελλάδα
Pfizer Ελλάς A.E.
Τηλ: +30 210 6785800

España
Pfizer, S.L.
Tel: +34 91 490 99 00

France
Pfizer
Tél: +33 (0)1 58 07 34 40

Hrvatska
Pfizer Croatia d.o.o.
Tel: +385 1 3908 777

Ireland
Pfizer Healthcare Ireland Unlimited Company
Tel: +1800 633 363 (toll free)
Tel: +44 (0)1304 616161

Ísland
Icepharma hf.
Sími: +354 540 8000

Italia
Pfizer S.r.l.
Tel: +39 06 33 18 21

Κύπρος
Pfizer Ελλάς A.E. (Cyprus Branch)
Τηλ: +357 22817690

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
Tel: + 371 670 35 775

Nederland
Pfizer bv
Tel: +31 (0)800 63 34 636

Norge
Pfizer AS
Tlf: +47 67 52 61 00

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp. z o.o.
Tel.: +48 22 335 61 00

Portugal
Laboratórios Pfizer, Lda.
Tel: +351 21 423 5500

România
Pfizer Romania S.R.L.
Tel: +40 (0) 21 207 28 00

Slovenija
Pfizer Luxembourg SARL
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Tel: +386 (0)1 52 11 400

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: + 421 2 3355 5500

Suomi/Finland
Pfizer Oy
Puh/Tel: +358 (0)9 430 040

Sverige
Pfizer AB
Tel: +46 (0)8 550 520 00

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

INSTRUCTIONS FOR USE
Hympavzi 150 mg solution for injection in pre-filled pen

This 'Instructions for Use' contains information on how to inject Hympavzi.

Read this 'Instructions for Use' carefully before using Hympavzi pre-filled pen and each time you get a refill prescription as there may be new information.

Your doctor, nurse or pharmacist should show you or your caregiver how to prepare and inject a dose of Hympavzi the right way before you use it for the first time.

Do not inject yourself or someone else until you have been shown how to inject Hympavzi.

Important Information

- Each Hympavzi pre-filled pen is a single-dose pre-filled pen (called "pen" in this 'Instructions for Use'). The Hympavzi pre-filled pen contains 150 mg of Hympavzi for injection under the skin (subcutaneously).
- **Do not** inject Hympavzi into a vein or muscle.
- **Do not** shake Hympavzi.
- To help you remember when to inject Hympavzi, you can mark your calendar ahead of time. Call your doctor, nurse or pharmacist if you or your caregiver have any questions about the right way to inject Hympavzi.

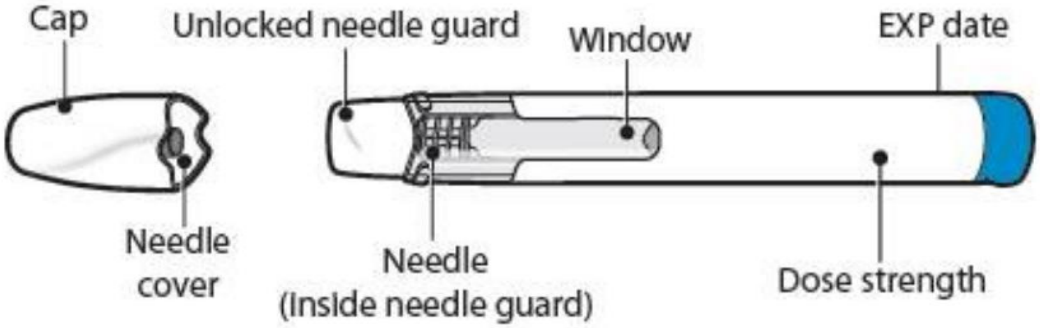
How To Store Hympavzi

- Store unused Hympavzi in the refrigerator between 2 °C to 8 °C. Do not freeze Hympavzi. Store Hympavzi in its original carton to protect from direct light.
- If necessary, Hympavzi may be stored in its original carton at room temperature up to 30 °C for up to 7 days. **Do not** use Hympavzi if it has been out of the refrigerator for longer than 7 days. Throw away (dispose of) any Hympavzi that has been kept at room temperature for longer than 7 days.
- **Do not** use past the expiry date printed on the Hympavzi pre-filled pen.
- **Keep Hympavzi and all medicines out of the reach of children.**

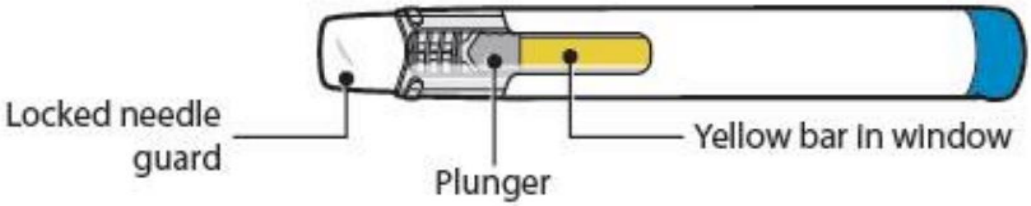
Supplies Needed For Hympavzi Injection

Gather the following supplies on a clean flat surface:
- 1 Hympavzi pre-filled pen.
- 1 alcohol swab (not included).
- 1 cotton ball or gauze pad (not included).
- 1 sharps disposal container for pen disposal (not included).

Hympavzi pre-filled pen BEFORE use:



Hympavzi pre-filled pen AFTER use:



Preparation Steps

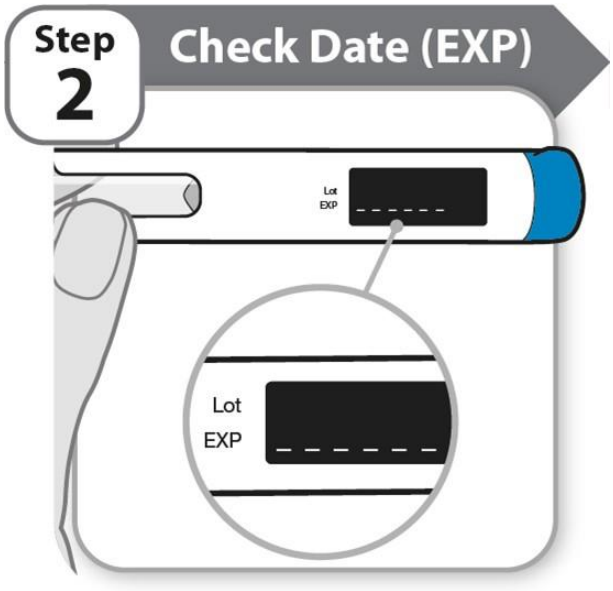
Step 1 – Getting Ready

- **Remove** the pen from its carton and keep out of direct sunlight.
- **Make sure** the name Hympavzi appears on the carton and pen label.
- **Check the pen** for any visible damage such as cracks or leaks.
- **Wash and dry** your hands.
- **Do not remove the cap until you are ready to inject.**
- **Throw away (dispose of)** the pen if it is damaged, or if the pen or the carton containing the pen has been dropped.
- **Do not** use the pen if:
  - it has been stored in direct light. Exposure to room light during dose preparation and injection is acceptable.
  - it has been frozen or thawed or it has been out of the refrigerator for more than 7 days.
- **Do not** shake the pen. Shaking can damage Hympavzi.

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

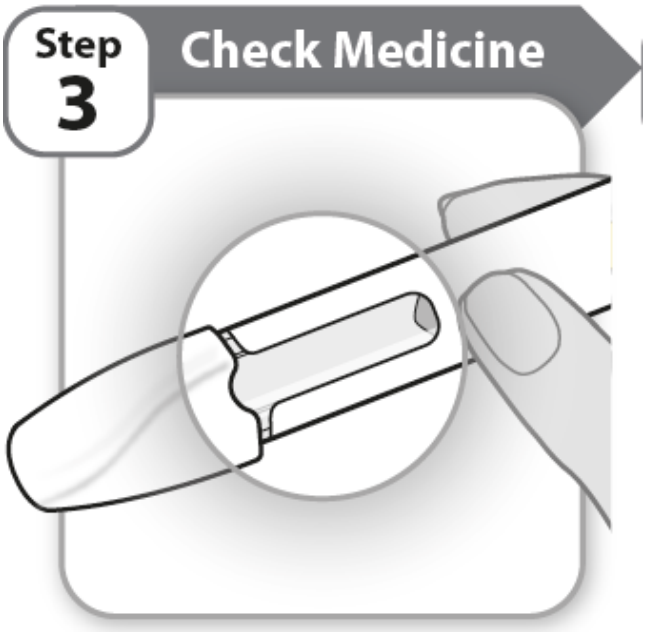
Do not use any other methods to warm up the pen, such as warming the pen in a microwave or hot water.

Step 2 – Check Date (EXP)



- **Check** the expiry date (EXP) printed on the pen label.
- **Do not** use if the expiry date has passed.

Step 3 – Check Medicine

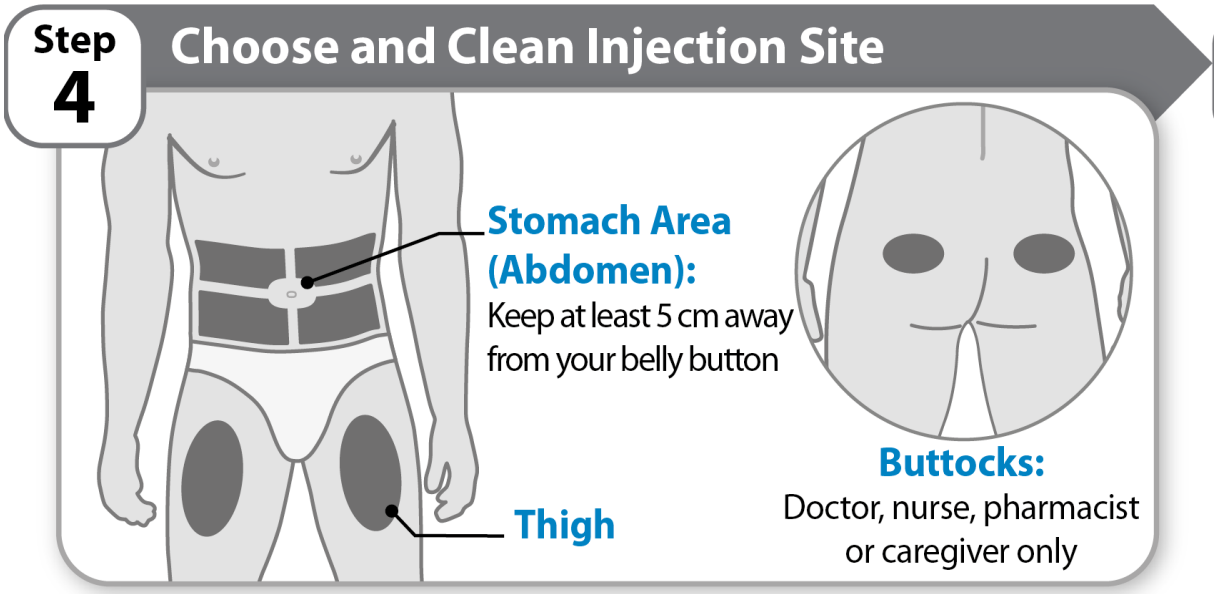


- **Look** carefully at the medicine through the window on the pen.
  - The medicine should be clear and colourless to light yellow.
  - **Do not** use the pen if the medicine is cloudy, dark yellow, or contains flakes or particles.

Note: It is normal to see air bubbles in the window.

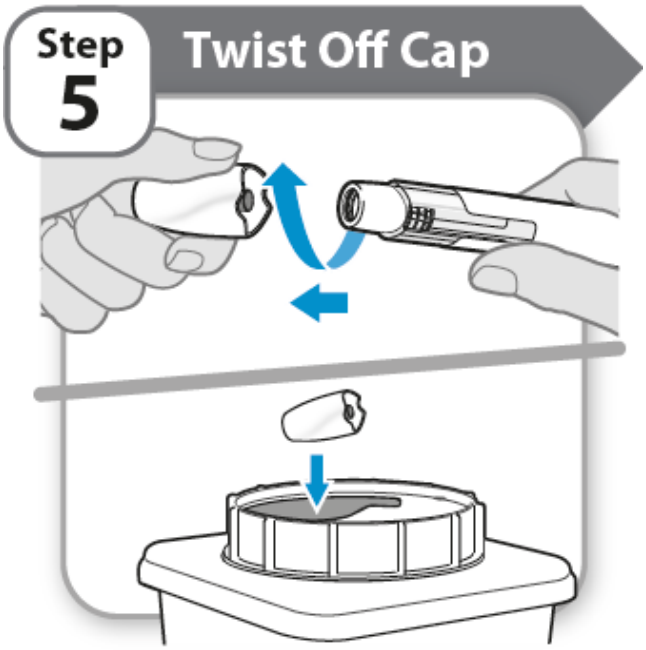
If you have any questions about the medicine, contact your doctor, nurse or pharmacist.

Step 4 – Choose and Clean Injection Site



- **Choose** an injection site on your stomach area (abdomen) or thigh unless a different site has been suggested by your doctor, nurse or pharmacist. Hympavzi may also be injected into your buttocks by a doctor, nurse, pharmacist or caregiver only. Keep at least 5 cm away from your belly button.
- **Change** the injection site each time you give yourself an injection of Hympavzi. You may use the same area of your body, but be sure to choose a different injection site in that area.
- **Clean** the injection site with soap and water, or an alcohol swab if convenient.
- **Allow** the site to dry. **Do not** touch, fan or blow on the cleaned injection site.
- **Do not** inject Hympavzi into bony areas or areas on your skin that are bruised, red, sore (tender) or hard. Avoid injecting into areas with scars or stretch marks.
- **Do not** inject Hympavzi into a vein or muscle.
- **Do not** inject Hympavzi through your clothes.

Step 5 – Twist Off Cap



- **Twist and pull** off the cap.
- **Put** the cap into a sharps disposal container right away. You will not need it again.

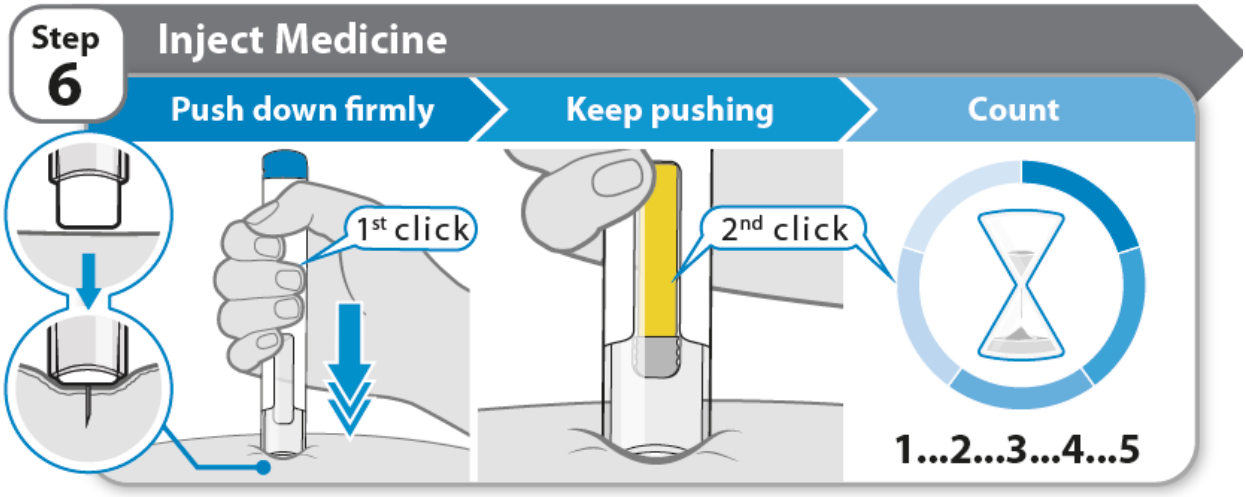
Note:
- It is normal to see a few drops of medicine at the needle tip.
- The needle cover will stay inside the cap after cap removal.

Caution: Handle the pen with care as it contains a needle.

Do not put, or press your hand over the needle guard. Doing so may result in a needle injury.

Injection Steps

Step 6 – Inject Medicine



- **Push** the pen **down firmly** against your skin at a 90° angle and **keep pushing** until the injection is complete (Step 7). You will hear the **1st click** when the injection starts.
- **Keep pushing** the pen firmly against your skin while the yellow bar moves across the window. You will hear a **2nd click** when the injection is **almost** complete.
- **Count slowly to 5 after you hear the 2nd click** to make sure you get a full dose.

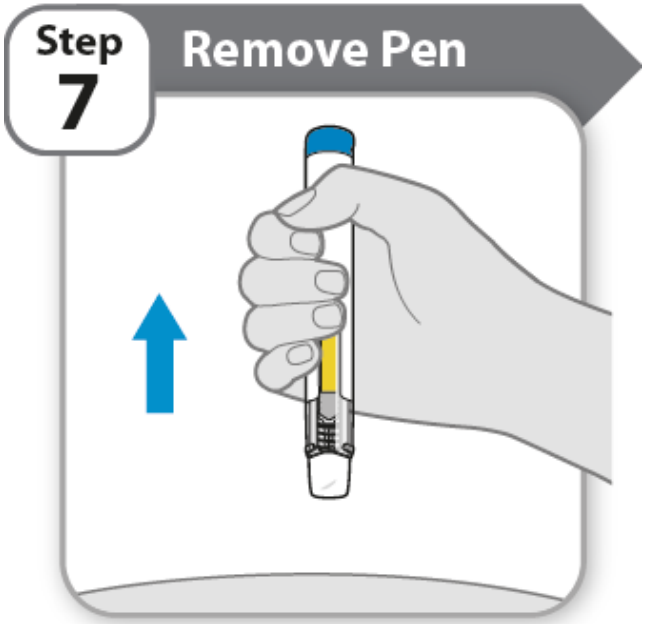
Do not remove the pen from your skin until you have counted slowly to 5 after you hear the 2nd click and until the yellow marker completely fills the window.

Note: The needle goes into your skin as you push the pen down. Your doctor, nurse or pharmacist may suggest gently pinching your skin while you inject.

Note: If you do not hear a click when pushing the pen against your skin, try pushing down harder. If you still cannot start the injection, get a new Hympavzi pre-filled pen.

Caution: If you change your mind where to inject after inserting the needle into your skin, you will need to throw away (dispose of) the pen and get a new Hympavzi pre-filled pen.

Step 7 – Remove Pen

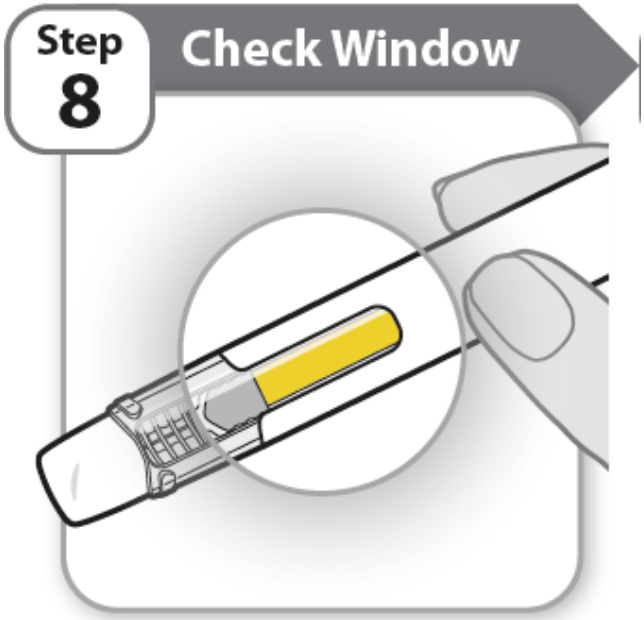


- **Remove** the pen from your skin.
  - If you see a small drop of medicine on your skin, wait a little longer before removing the pen when you give your next injection.

Note: After you remove the pen from your skin, the needle will be automatically covered and the needle guard locked in place.

The pen cannot be reused.

Step 8 – Check Window



- **Check** the window to make sure all the medicine has been injected.

If the yellow bar is not in the position shown, this means you have not received a full dose. Call your doctor, nurse or pharmacist for help.

Do not inject another dose.

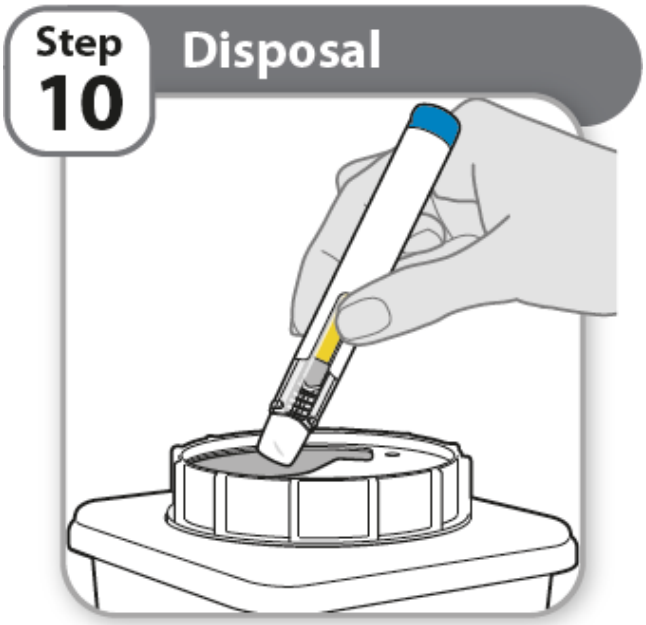
Step 9 – After Care



- **Press** lightly on the injection site for a few seconds with a clean cotton ball or gauze pad if you see a drop of blood.
- **Do not** rub the area.

Note: If bleeding does not stop, please contact your doctor, nurse or pharmacist.

Step 10 – Disposal



- **Put** the used pen in a sharps disposal container as instructed by your doctor, nurse or pharmacist and in accordance with local health and safety laws.
- **Do not** throw away (dispose of) pens in the household waste.

4. 臨床特性

4.1. 効能・効果

本剤は、以下の疾患を有する 12 歳以上かつ体重 35 kg 以上の患者における出血傾向の抑制を目的とした定期的投与を適応とする。

- 血友病 A（先天性 FVIII 欠乏症）：
  - 第 VIII 因子インヒビターを保有せず、重症（FVIII 活性が 1%未満）の患者
  - 第 VIII 因子インヒビターを保有する患者
- 血友病 B（先天性 FIX 欠乏症）：
  - 第 IX 因子インヒビターを保有せず、重症（FIX 活性が 1%未満）の患者
  - 第 IX 因子インヒビターを保有する患者

4.2. 用法・用量

本剤は血友病の治療経験のある医療従事者の監督下で投与すること。投与は非出血時に行うこと。

用量

12 歳以上かつ体重 35 kg 以上の患者には、初回負荷用量として 300 mg を皮下投与し、その後は 150 mg を週 1 回皮下投与する。投与時刻は問わない。

投与期間

本剤は長期間の予防的投与を目的としたものである。

投与期間中の用量調整

体重 50 kg 以上の患者で出血傾向の抑制が不十分と医療従事者が判断した場合には、300 mg 週 1 回皮下投与への増量を検討してもよい。週あたりの投与量は 300 mg を超えてはならない。

出血の治療に関するガイダンス

出血の治療を目的とした本剤の追加的投与は行わないこと。出血が認められた場合の治療については 4.4 項を参照のこと。

急性の重度疾患を有する患者の管理

組織因子の発現増加を伴う重篤な感染症、敗血症、外傷、挫滅及びがんなどの急性の重度疾患では、組織因子経路インヒビター（TFPI）阻害薬の併用は炎症性反応を増強し、特に血栓症の副作用リスクをもたらす可能性がある（4.4 項参照）。

急性の重度疾患の治療は各国の標準治療に従って行うこととし、本剤の投与を継続する場合は、投与に伴う潜在的リスクを比較検討した上で行う。急性の重度疾患を有する患者では、マルスタシマブを投与する際に副作用及び血栓塞栓症の発現に対する追加的なモニタリングが必要となる場合がある。血栓性事象を示す臨床症状、画像所見及び（又は）臨床検査所見が認められた場合は、本剤を一時的に休薬し、臨床的必要性に応じて管理する。医療従事者が患者が臨床的に回復したと判断した場合には、本剤の投与を再開することができる（以下の「投与忘れ」の項参照）。

投与忘れ

150 mg の維持用量を投与中の患者

投与を忘れた場合は、次回投与予定日前に可能な限り速やかに忘れた投与分を投与し、その後は通常の 150 mg 週 1 回皮下投与スケジュール（投与忘れ前と同じスケジュール、又は忘れた投与分を実施した日を基準とした新しいスケジュール）にて再開する。

投与再開までの期間が直近の投与日から 13 日を超える場合、再開時は負荷用量として 300 mg を皮下投与し、その後は 150 mg 週 1 回皮下投与を再開する。

300 mg の維持用量を投与中の患者

1 回分以上の投与を忘れた場合は、次回投与予定日前に可能な限り速やかに忘れた投与分を投与し、その後は通常の 300 mg 週 1 回皮下投与スケジュール（投与忘れ前と同じスケジュール、又は忘れた投与分を実施した日を基準とした新しいスケジュール）にて再開する。

本剤への切り替え

血液凝固因子補充療法又はバイパス製剤から本剤に切り替える場合：本剤の投与を開始する前に血液凝固因子製剤（FVIII 又は FIX）又はバイパス製剤［例：遺伝子組換え活性型第 VII 因子製剤（rFVIIa）又は活性型プロトロンビン複合体製剤（aPCC）］の投与を中止すること。血液凝固因子製剤又はバイパス製剤の中止後はいつでも本剤の投与を開始することができる。

血液凝固因子製剤以外の血友病治療薬から本剤に切り替える場合：その他の血液凝固因子製剤以外の血友病治療薬から本剤に切り替える場合の指針となる臨床試験データは得られていない。休薬期間は検討されていないが、方法の一つとして、その製剤の半減期に基づき適切な休薬期間（少なくとも半減期の 5 倍の期間）を設け、本剤の投与を開始する。休薬期間中は、必要に応じて血液凝固因子製剤又はバイパス製剤による止血治療を行う。

特定の集団

肝機能障害

軽度の肝機能障害を有する患者での用量調整は不要である（5.2 項参照）。中等度又は重度の肝機能障害を有する患者を対象としたマルスタシマブの臨床試験は実施していない。

腎機能障害

軽度の腎機能障害を有する患者での用量調整は不要である（5.2 項参照）。中等度又は重度の腎機能障害を有する患者を対象としたマルスタシマブの臨床試験は実施していない。

高齢者

65 歳以上の患者での用量調整は推奨されない（5.2 項参照）。

小児集団

安全性上の問題の可能性があることから、1 歳未満の小児では本剤を使用してはならない。12 歳未満の小児患者及び体重 35 kg 未満の青年患者におけるマルスタシマブの安全性及び有効性は確立されておらず、データは得られていない。

周術期の管理

外科的処置におけるマルスタシマブの安全性及び有効性は正式に評価されていない。臨床試験において、患者は小手術を受ける際に本剤の予防的投与を中止しなかった。

大手術を行う場合は、少なくとも 7 日前に本剤の投与を中断し、血液凝固因子製剤又はバイパス製剤を用いた各国の標準治療に基づく管理を開始し、周術期に上昇する可能性のある静脈血栓症のリスクを管理するための措置を行うことが推奨される。大手術を受ける血友病患者に血液凝固因子製剤又はバイパス製剤を投与する際は、当該製剤の製品情報をガイドラインとして参照すること。本剤の投与を再開する場合は、術後の血栓塞栓症危険因子の有無や、その他の止血製剤及び併用薬の使用を含めて、患者の全身状態を考慮すること（上記「投与忘れ」の項参照）。

免疫寛容導入療法（ITI）

継続的な ITI を導入している患者におけるマルスタシマブの安全性及び有効性は確立されておらず、データは得られていない。

投与方法

本剤は皮下投与でのみ使用可能である。

本剤は医療従事者の指導の下で使用すること。患者又は介護者は、皮下注射について適切な訓練を実施したのち、妥当であると医療従事者が判断した場合に本剤の投与を行うことができる。

皮下投与する前に本剤を冷蔵庫から取り出し、直射日光を避け、外箱に入れたまま 15～30 分間かけて室温に戻しておくこと（6.4 項及び 6.6 項参照）。熱湯や電子レンジなどの熱源を用いて本剤を温めないこと。

推奨される投与部位は腹部（臍から少なくとも 5 cm 離れた部位）及び大腿部である。必要な場合はその他の部位への投与も許容される。上腕部（プレフィルドシリンジのみ）及び臀部（プ

レフィルドペン型注入器のみ）への投与は介護者又は医療従事者のみが行う。骨ばった部位や内出血、発赤、圧痛、硬結、瘢痕又は伸展裂創などが認められる部位には投与しないこと。

300 mg の負荷投与を行う場合は、150 mg をそれぞれ異なる部位に投与すること。

投与ごとに投与部位を変えることが望ましい。

静脈内又は筋肉内への投与は行わないこと。

本剤による治療期間中に他の製剤の皮下投与を行う場合は、異なる部位に投与することが望ましい。

本剤の投与に関する総合的な説明については、6.6 項及び添付文書の最後に記載した「使用説明書」を参照のこと。

4.3. 禁忌

有効成分又は 6.1 項に記載されている成分のいずれかに対する過敏症

4.4. 特別な警告及び使用上の注意

トレーサビリティ

生物学的製剤のトレーサビリティを向上させるために、投与した製品の名称及びバッチ番号を明確に記録すること。

血栓塞栓性事象

TFPI の阻害作用を取り除くと凝固能が高まり、血栓塞栓性事象に対する患者の個々のリスク又は多因子的なリスクの一因となる。本剤の臨床試験において塞栓性を含む動脈及び静脈血栓性事象が報告された（4.8 項参照）。これらの事象は、血栓塞栓性の複数の危険因子を有する患者に発現した。以下の患者では、本剤の使用により血栓塞栓性事象のリスクが高まる可能性がある。

- 冠動脈疾患、静脈血栓症、動脈血栓症又は虚血性疾患の既往歴を有する患者
- 血栓塞栓症の既知の危険因子［遺伝性血栓症素因（例：第 V 因子ライデン変異）を含むがこれらに限らない］を有する患者、長期間の不動状態にある患者、肥満患者、喫煙者
- 組織因子の発現増加を伴う急性の重度疾患（重篤な感染症、敗血症、外傷、挫滅、がんなど）を発症している患者
- 周術期の管理下にある及び（又は）手術中の患者（4.2 項参照）。周術期は、本剤と他の止血剤の併用投与により血栓症のリスクが高まる可能性がある。

血栓塞栓性事象の既往歴を有する患者を対象としたマルスタシマブの臨床試験は実施しておらず（5.1 項参照）、急性の重度疾患を有する患者でのマルスタシマブの使用経験は限られている。

血栓塞栓性事象の既往歴を有する患者、血栓塞栓症の既知の危険因子を有する患者又は急性の重度疾患を発症している患者では、本剤を使用することのベネフィット及びリスクを考慮する必要がある。リスクを有する患者については、血栓症の初期徴候の有無を観察し、現行の推奨事項及び標準治療に従って血栓塞栓症に対する予防措置を講じること。血栓塞栓症を示す診断所見が認められた場合は本剤の予防的投与を中断し、臨床的に適切に管理すること。

マルスタシマブを含む抗組織因子経路インヒビター（抗 TFPI）抗体の使用に関しては、止血剤（バイパス製剤など）の追加投与（時間的に近い場合）による血栓塞栓性合併症の発現と関連することが示されている。マルスタシマブの投与を受けている患者に出血の治療薬として FVIII 製剤及び FIX 製剤、又はバイパス製剤を投与したときの安全性に問題は認められていない。本剤の予防的投与を受けている患者に FVIII 製剤、FIX 製剤又はバイパス製剤を使用する場合は、これらの製剤の表示に従って最小有効量を用いることが推奨される。血栓塞栓性事象の徴候及び症状の発現について患者に説明し、それらの発現について観察すること。血栓塞栓性事象が疑われる場合、本剤の投与を中止し、適切な内科的治療を開始すること。

出血の治療に関するガイダンス

FVIII 製剤及び FIX 製剤、又はバイパス製剤（例：rFVIIa 又は aPCC）は、本剤の投与を受けている患者での出血の治療薬として投与することが可能である。出血の治療を目的とした本剤の追加的投与は行わないこと。医療従事者は、必要な場合は、すべての患者及び（又は）介護者に対して、本剤の予防的投与の実施中に使用する血液凝固因子製剤又はバイパス製剤の用量及び投与スケジュールについて、説明すること。

出血時に FVIII 製剤及び FIX 製剤、又はバイパス製剤を用いて治療する場合は、各製剤の製品添付文書に基づく最小有効量の使用が推奨される。医療従事者は、使用する凝固因子製剤又はバイパス製剤の製品情報を参照すること。rFVIIa については、1 回投与あたり体重 1 kg あたり 90 µg、及び最短投与間隔を 2 時間とすることが推奨される。aPCC については、24 時間に体重 1 kg あたり最大 100U を上限とすることが推奨される。

過敏症反応

マルスタシマブの投与を受けた患者において、薬物過敏症の可能性のある発疹及びそう痒症の皮膚反応が認められている（4.8 項参照）。本剤を投与した患者で重度の過敏症反応が認められた場合は、本剤の投与を中止して直ちに救急治療を受けるよう指導する。

凝固検査値に及ぼすマルスタシマブの影響

マルスタシマブの投与は、活性化部分トロンボプラスチン時間（aPTT）及びプロトロンビン時間（PT）を含め、凝固検査の基準値に臨床的に意味のある影響を及ぼすものではない。

添加剤

ポリソルベート

本剤はポリソルベート 80 を含有する。ポリソルベート 80 は過敏症反応を引き起こすことがある。

ナトリウム

本剤は 1 mL 中に 1 mmol（23 mg）未満のナトリウムを含有し、実質的に「ナトリウム非含有」である。

4.5. 他の医薬品との相互作用及びその他の形態の相互作用

マルスタシマブの薬物相互作用試験は実施していない。

In vitro の非臨床薬力学的薬物相互作用試験において、出血時の出血治療におけるマルスタシマブとバイパス製剤（例：rFVIIa 又は aPCC）の併用使用を支持する結果が得られている。マルスタシマブと rFVIIa 又は aPCC の併用投与（インヒビターを保有する血友病 A 及び B 患者の血漿中）により、マルスタシマブ単剤投与時と比較してトロンビン生成が増加したが、マルスタシマブ単剤投与を受けた非血友病患者の血漿中で到達した最高トロンビン濃度を超えることはなかった。場合によっては、トロンビン濃度は非血友病患者の正常な血漿で報告された範囲内であった。

正常な第 VIII 因子及び第 IX 因子レベルを有するラットを用いた in vivo の非臨床薬力学的薬物相互作用試験においても、出血時の出血治療におけるマルスタシマブと最高臨床用量 90 µg/kg 以下での rFVIIa 又は最高臨床用量 100 単位/kg での aPCC の併用使用を支持する結果が得られている。高用量の rFVIIa で正常に止血されたラットでは、肺及び注射部位での急性血栓／塞栓の発現率及び（又は）重症度の増加が認められた（5.3 項参照）。

マルスタシマブの予防投与を受けている患者における出血時の出血治療に関する血液凝固因子製剤又はバイパス製剤のガイダンスについては、4.4 項を参照のこと。

マルスタシマブはモノクローナル抗体（mAb）であることから、異化経路を介して消失すると考えられる。したがって、異化経路以外の経路で消失する併用薬との相互作用によりマルスタシマブのクリアランスが影響を受ける可能性は低い。また、マルスタシマブなどの生物学的製剤がシトクロム P450 の発現に間接的に影響を及ぼす可能性も低い。

4.6. 受胎能、妊娠及び授乳

<u>妊娠可能な女性</u>

妊娠可能な女性は、本剤の投与を受ける場合、本剤の投与期間中及び投与中止後少なくとも 1 カ月間は効果の高い避妊法を使用すること。

<u>妊娠</u>

妊婦を対象としたマルスタシマブの臨床試験は実施していない。動物を用いたマルスタシマブの生殖発生毒性試験は実施していない。マルスタシマブを妊婦に投与したときに胎児に害を及ぼすかどうか、あるいは生殖能に影響を及ぼすか否かは明らかになっていない。血栓症のリスクが妊娠中及び分娩後に高まること並びに様々な妊娠合併症が播種性血管内凝固（DIC）のリスク上昇に関連していることを考慮し、妊娠中は、母親に対する有益性が胎児への危険性を上回る場合にのみ本剤を使用すること。

授乳

マルスタシマブがヒトの乳汁中に移行するかは明らかになっていない。マルスタシマブの乳汁産生への影響又は母乳中への移行を評価する臨床試験は実施していない。ヒト IgG は、出生後数日の間母乳中へ移行し、その後急速に濃度が低下することが知られている。そのため、この短期間での乳児へのリスクは除外できない。その後は、臨床的必要性に応じて授乳中にマルスタシマブを投与することは可能である。

生殖能

動物を用いた試験では、生殖能に対する直接的又は間接的な有害作用は認められていない（5.3 項参照）。ヒトにおける生殖能のデータは得られていない。したがって、男性及び女性の生殖能に対するマルスタシマブの影響は不明である。

4.7. 運転及び機械操作能力への影響

本剤は、運転及び機械操作能力に影響を及ぼさないか、ほとんど影響を及ぼさない。

4.8. 望ましくない反応（Undesirable effects）

安全性プロファイルの要約

マルスタシマブの全体的な安全性プロファイルは、臨床試験の併合データに基づいている。マルスタシマブを用いた臨床試験で報告された主な重篤な副作用（ADR）は血栓症（0.6%）であった（4.4 項参照）。

マルスタシマブの投与後に報告された主な副作用は注射部位反応（ISR）（11.4%）であった。

副作用の一覧表

Table 1 に示した安全性データは、安全性及び有効性を検討する第 3 相試験（BASIS 試験）及び BASIS 試験から非盲検継続投与（OLE）試験に移行した患者で得られた併合データに基づいている（5.1 項参照）。この第 3 相主要試験の 12 カ月の実薬投与期間に得られたデータは、インヒビターを保有する（30.5%）又は保有しない（69.5%）血友病 A 又は B の男性患者 167 例にマルスタシマブを週 1 回投与したときのものである。167 例の患者のうち、135 例（80.8%）が成人（18 歳以上）、32 例（19.2%）が青年（12 歳以上 18 歳未満）であった。12 カ月の投与期間を完了した 159 例のうち 154 例が続いて実施中の OLE 試験に移行した。全投与期間の中央値は 1225 日（範囲：28～1659 日）であった。

マルスタシマブの予防的投与を受けた患者で報告された副作用を Table 1 に要約する。副作用は器官別大分類（SOC）及び発現頻度別に示した。発現頻度の分類は次の慣例を用いて示す：Very common（10%以上）、Common（1%以上 10%未満）、Uncommon（0.1%以上 1%未満）、Rare（0.01%以上 0.1%未満）、Very rare（0.01%未満）、not known（利用可能なデータからは推定できない）。副作用は、発現頻度の各分類内で重症度の高い順に示した。

Table 1　　副作用

器官別大分類	副作用	発現頻度
神経系障害	頭痛 [a]	Common
血管障害	高血圧 血栓塞栓性事象（血栓症 [b]）	Common Uncommon
皮膚および皮下組織障害	発疹 そう痒症	Common Common
一般・全身障害および投与部位の状態	注射部位反応 [c]	Very common

a. 頭痛及び片頭痛の両方が含まれる。
b. OLE 試験で報告された ADR。
c. 「特定の副作用に関する記述」を参照のこと。

特定の副作用に関する記述

注射部位反応

マルスタシマブの投与を受けた患者の 19 例（11.4%）で ISR が報告された。マルスタシマブの臨床試験で認められた ISR の大多数は一過性であり、軽度から中等度であると報告された。ISR により用量調整又は投与中止に至った症例はなかった。ISR には、注射部位内出血、注射部位紅斑、注射部位血腫、注射部位出血、注射部位硬結、注射部位浮腫、注射部位疼痛、注射部位そう痒感及び注射部位腫脹が含まれる。

発疹

マルスタシマブの投与を受けた患者の 6 例（3.6%）で発疹が報告された。

インヒビターを保有し、外因性第 IX 因子に対するアレルギー反応の既往を持つ重症血友病 B 患者の 1 例において、投与開始から約 9 カ月後に重度の発疹が報告された。症状改善のために長期の経口コルチコステロイド投与を要し、マルスタシマブの投与は中止された。

小児集団

臨床試験には青年患者（12 歳以上 18 歳未満）32 例からなる小児集団が含まれた。マルスタシマブの安全性プロファイルは青年患者と成人患者で全体的に一貫していた。

副作用が疑われる事象の報告

本剤承認後に副作用が疑われる症例を報告することは重要である。これにより本剤のベネフィット・リスクバランスのモニタリングを継続することができる。副作用が疑われる場合には Appendix V の国の報告制度を用いて、報告するよう医療従事者に依頼する。

4.9. 過量投与

マルスタシマブの過量投与の経験は限られている。

初期の臨床試験で、マルスタシマブ 450 mg を週 1 回、最長 3 カ月間皮下投与した体重 50 kg 以上の少数の成人患者では、重篤な有害事象は発現しなかった。しかし、少人数であったため、これよりも長期間の高用量投与の影響は明らかではない。推奨用量を超える投与では凝固能亢進を引き起こす可能性がある。

患者は、誤って過量投与を受けた場合、直ちに担当の医療従事者に連絡し、慎重な経過観察を受けること。過量投与が生じた場合は、副作用及び（又は）凝固能亢進の徴候又は症状の有無を観察し、直ちに適切な対症療法を行う。

小児集団

12～17 歳の体重 50 kg 未満の青年患者を対象に 150 mg/週を超える用量を投与する臨床試験は実施していない。小児での過量投与は報告されていない。小児における過量投与の管理には上記の原則を適用する。

PREPARED BY PFIZER INC

CDS EFFECTIVE DATE: [redacted]-[redacted]-20[redacted]

Date of Superseded CDS: [redacted]-[redacted]-20[redacted]

MARSTACIMAB

CORE DATA SHEET

VERSION [redacted]

CDS 2～51ページは非公表のため省略

販　　売　　名	ヒムペブジ皮下注 150mgペン	アレモ皮下注 15mg アレモ皮下注 60mg アレモ皮下注 150mg アレモ皮下注 300mg
一　　般　　名	マルスタシマブ（遺伝子組換え）	コンシズマブ（遺伝子組換え）
会　　社　　名	ファイザー株式会社	ノボ ノルディスク ファーマ株式会社
効 能 ・ 効 果	先天性血友病患者における出血傾向の抑制	先天性血友病患者における出血傾向の抑制
作成・改訂年月	2026年XX月改訂（第X版）	2025年5月改訂（第3版）
備　　考	－	－

＊最新の添付文書を参照すること。

**2025年5月改訂（第3版）
*2024年6月改訂（第2版、効能変更）
貯　　法：凍結を避け、2～8℃に保存
有効期間：24ヵ月

抗TFPIモノクローナル抗体
コンシズマブ（遺伝子組換え）

アレモ®皮下注15mg
アレモ®皮下注60mg
アレモ®皮下注150mg
アレモ®皮下注300mg

Alhemo® Subcutaneous Injection

生物由来製品
処方箋医薬品注）

注）注意 － 医師等の処方箋により使用すること

日本標準商品分類番号	876349

	承認番号	販売開始
15mg	30500AMX00276000	－
60mg	30500AMX00277000	2024年5月
150mg	30500AMX00281000	2024年2月
300mg	30500AMX00278000	－

1. 警告

1.1 本剤の臨床試験において重篤な血栓塞栓性事象の発現が複数例に認められている。観察を十分に行い、血栓塞栓性事象が疑われる場合には本剤の投与を中止し、適切な処置を行うこと。また、患者に対し、血栓塞栓性事象の兆候や症状について十分説明すること。[8.1、8.3.1、9.1.2、11.1.2参照]

1.2 本剤は血友病治療に十分な知識・経験を持つ医師のもと、緊急時に十分対応できる医療機関で投与開始すること。[8.1、9.1.2、11.1.2参照]

1.3 本剤の投与開始に先立ち、患者又はその家族に危険性を十分説明し、同意を得た上で本剤を投与すること。

2. 禁忌（次の患者には投与しないこと）

本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

販売名		アレモ皮下注			
		15mg	60mg	150mg	300mg
容量	1筒	1.5mL	1.5mL	1.5mL	3mL
有効成分	コンシズマブ（遺伝子組換え）	15mg	60mg	150mg	300mg
添加剤	L-アルギニン塩酸塩	7.90mg			15.81mg
	L-ヒスチジン	7.68mg			15.36mg
	塩化ナトリウム	2.19mg			4.38mg
	精製白糖	76.9mg			153.9mg
	ポリソルベート80	0.37mg			0.75mg
	フェノール	5.25mg			10.5mg
	塩酸	適量			適量
	水酸化ナトリウム	適量			適量

本剤はチャイニーズハムスター卵巣細胞を用いて製造される。

3.2 製剤の性状

剤形・性状	注射剤 本剤は無色～微黄色の澄明～僅かに濁った液であり、半透明のタンパク質性微粒子が認められることがあるが、それ以外の微粒子を認めない。
pH	5.7～6.3
浸透圧比（生理食塩液に対する比）	約1

＊4. 効能又は効果

先天性血友病患者における出血傾向の抑制

＊5. 効能又は効果に関連する注意

本剤は、血液凝固第Ⅷ因子又は第Ⅸ因子に対するインヒビターの有無によらず有効性が確認されている。
[17.1.1-17.1.2参照]

6. 用法及び用量

通常、12歳以上の患者には、1日目に負荷投与としてコンシズマブ（遺伝子組換え）1mg/kgを皮下投与する。2日目以降は維持用量として1日1回、0.20mg/kgを皮下投与する。
なお、0.20mg/kgの投与を開始後、コンシズマブの血中濃度や患者の状態により、0.15mg/kgに減量又は0.25mg/kgに増量できる。

7. 用法及び用量に関連する注意

7.1 本剤投与開始後の維持用量の用量調節に際しては、以下の事項に留意すること。

7.1.1 本剤投与開始から4週を経過した時点でコンシズマブの血中濃度を確認すること。0.25mg/kgへの増量は血中濃度が200ng/mL未満である場合に、0.15mg/kgへの減量は目安として血中濃度が4000ng/mL超である場合に、行うことができる。

7.1.2 7.1.1に基づく用量調節は血中濃度の結果入手後早期（本剤投与開始から8週以内目安）が望ましい。

7.1.3 患者の臨床症状により、必要に応じて本薬の血中濃度を測定し、追加の用量調節も考慮すること。

7.1.4 本薬の血中濃度が特に高くなった場合に血栓塞栓性事象の発現リスクが高まるおそれがある。

** 7.2 血中濃度の測定にあたっては、承認された体外診断用医薬品を用いること。なお、承認された体外診断用医薬品に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html

7.3 本剤は、出血傾向の抑制を目的とした定期的な投与のみに使用し、出血時の止血を目的とした投与は行わないこと。

＊7.4 1日1回投与を遵守すること。

＊7.5 本剤の投与中止により数日間で血中コンシズマブ濃度が低下し、有効性が低下するおそれがある。投与を1回忘れた場合は、追加の負荷用量は投与せず、維持用量で1日1回投与を再開すること。投与を連続して2回以上忘れた場合は、速やかに医療機関へ連絡するよう患者にあらかじめ指導しておき、出血リスク等の患者の状態を確認した上で、再開時の用量（増量又は負荷投与を含む）を指示すること。

8. 重要な基本的注意

8.1 臨床試験において、血栓塞栓症が認められている。血栓塞栓性事象があらわれることがあるので、血栓塞栓性事象の既往又は危険因子の有無を慎重に確認した上で、本剤の投与を開始すること。また、患者に対し、血栓塞栓性事象の兆候や症状について十分説明し、以下の事項の注意の重要性について理解を得た上で投与を開始すること。[1.1、1.2、9.1.2、11.1.2参照]

＊8.2 活性型第Ⅶ因子製剤の投与は本剤投与開始12時間前までに、活性型プロトロンビン複合体（乾燥人血液凝固因子抗体迂回活性複合体）製剤及び乾燥濃縮人血液凝固第X因子加活性化第Ⅶ因子製剤の投与は本剤投与開始48時間前までに中止すること。半減期標準型の第Ⅷ因子製剤及び第Ⅸ因子製剤の定期的な投与は、本剤投与開始24時間前までに中止すること。半減期延長型など、その他の製剤から本剤へ切替える場合には、切替え前の製剤の半減期を考慮すること。

MOS000419

8.3　本剤投与中に出血が発生した場合は、以下の点に注意すること。

＊ 8.3.1 軽度から中等度の出血に対して、バイパス止血製剤（活性型第Ⅶ因子製剤、活性型プロトロンビン複合体製剤、乾燥濃縮人血液凝固第Ｘ因子加活性化第Ⅶ因子製剤）、第Ⅷ因子製剤又は第Ⅸ因子製剤による治療を行う場合は、承認されている最低用量を目安として、出血部位や程度に応じて投与量や投与期間を判断すること。活性型プロトロンビン複合体製剤については、24 時間以内の最高用量は体重 1kg 当たり 100 単位を上限とすることが望ましい。また、血液凝固系検査やその他の関連する診断方法等により患者の状態を注意深く確認すること。異常が認められた場合には本剤の投与を中止し、適切な処置を行うこと。[1.1、11.1.2 参照]

＊ 8.3.2 本剤投与中にバイパス止血製剤、第Ⅷ因子製剤又は第Ⅸ因子製剤の使用が必要になった場合に備え、バイパス止血製剤、第Ⅷ因子製剤又は第Ⅸ因子製剤の投与量や投与間隔等をあらかじめ患者に指導すること。

8.3.3 他剤による出血時治療を行っている場合でも本剤の用量を変更しないこと。

8.3.4 重度の出血が生じた場合は、血友病や出血性疾患の治療経験をもつ医師に相談すること。

8.4　大手術が必要な場合には、血友病や出血性疾患の治療経験をもつ医師に相談すること。大手術時の使用経験は限られているため、通常は大手術時には本剤による治療を中断することが望ましい。なお、小手術時に本剤の用量を調節する必要はない。

8.5　本剤の自己注射にあたっては、以下の点に留意すること。

- 投与法について十分な教育訓練を実施したのち、患者自ら確実に投与できることを確認した上で、医師の管理指導の下で実施すること。
- 患者に対し、全ての器具の安全な廃棄方法について指導を徹底すること。
- 添付されている取扱説明書を必ず読むよう患者に指導すること。
- 患者又はその家族に対し、自己注射後に何らかの異常が認められた場合は、速やかに医療機関へ連絡するよう指導すること。

9. 特定の背景を有する患者に関する注意

9.1　合併症・既往歴等のある患者

9.1.1 組織因子が過剰に発現している状態にある患者

組織因子が過剰に発現している状態（進行したアテローム性疾患、癌、挫滅、敗血症、炎症病態等）では、本剤投与により血栓塞栓性事象又は播種性血管内凝固症候群（DIC）のリスクが高まる可能性がある。

9.1.2 血栓塞栓性事象の既往又は危険因子を有する患者

治療上の有益性と危険性を十分考慮すること。[1.1、1.2、8.1、11.1.2 参照]

9.4　生殖能を有する者

妊娠可能な女性には、本剤投与中及び投与終了後 7 週間は適切な避妊法を用いるよう指導すること。

9.5　妊婦

妊婦又は妊娠している可能性のある女性には治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。生殖発生毒性試験は実施していない。一般に、ヒト IgG は胎盤を通過することが知られている。

9.6　授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤のヒト乳汁中への移行性については不明であるが、一般にヒト IgG は母乳に分泌されることが知られている。

9.7　小児等

12 歳未満の小児等を対象とした臨床試験は実施していない。

9.8　高齢者

患者の状態を観察しながら慎重に投与すること。一般に生理機能が低下している。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1　重大な副作用

11.1.1 ショック、アナフィラキシー（いずれも頻度不明）

そう痒、全身性蕁麻疹、胸部圧迫感、喘鳴、低血圧等の症状が認められた場合には投与を中止し、適切な処置を行うこと。

＊ **11.1.2 血栓塞栓性事象（1.1%）**

観察を十分に行い、血栓塞栓性事象が疑われる場合には本剤の投与を中止し、適切な処置を行うこと。[1.1、1.2、8.1、8.3.1、9.1.2 参照]

＊ 11.2　その他の副作用

	5%以上	1%～5%未満	1%未満
免疫系障害			過敏症
皮膚および皮下組織障害		そう痒症	
一般・全身障害および投与部位の状態	注射部位反応（注射部位紅斑、注射部位蕁麻疹、注射部位血腫、注射部位そう痒感、注射部位内出血、注射部位発疹及び注射部位疼痛等）(16.2%)		
臨床検査	プロトロンビンフラグメント１・２増加、Ｄダイマー増加	線維素溶解(Ｄダイマー及びプロトロンビンフラグメント１・２の増加)	

12. 臨床検査結果に及ぼす影響

本剤存在下で、プロトロンビン時間に基づく凝固法により FⅧ活性が高く測定される。

14. 適用上の注意

14.1　薬剤投与前の注意

14.1.1 本剤は無色～微黄色の澄明～僅かに濁った液であり、半透明の微粒子が認められることがある。薬液が変色している場合には、本剤を使用しないこと。

14.1.2 本剤と A 型専用注射針との装着時に液漏れ等の不具合が認められた場合には、新しい注射針に取り替える等の処置方法を患者に十分指導すること。

14.2　薬剤投与時の注意

14.2.1 投与時

本剤は、JIS T 3226-2 に準拠した 32G・4mm の A 型専用注射針を用いて使用すること。本剤は A 型専用注射針との適合性の確認をペンニードルプラスで行っている。針の長さが 4 mmを超える A 型専用注射針を使用する場合や子供又は痩躯患者が使用する場合は、筋肉内注射を避けるための処置（皮膚をつまんだ状態で注射するなど）を指導すること。

14.2.2 投与部位

腹部又は大腿部に皮下注射すること。注射箇所は毎回変更すること。皮膚が敏感な部位、あざ、発赤又は硬結が認められる部位あるいはほくろや傷がある部位には投与しないこと。

14.2.3 その他

(1)　本剤に薬液を補充しないこと。

(2)　本剤は製剤ごとに 1 人の患者が使用し、複数の患者と共有しないこと。

(3)　他の医薬品と混合しないこと。

14.3　薬剤投与後の注意

14.3.1 使用開始後は冷蔵庫又は室温（30℃以下）で保管し、4 週以内に使用すること。

14.3.2 汚染、感染及び液漏れ防止のため、注射針を付けたまま保管せず、注射の後は毎回注射針を廃棄すること。

15. その他の注意

15.1 臨床使用に基づく情報

＊15.1.1 本剤による治療期間〔4159試験：11週間、4255試験及び4310試験（76週間以上）、4311試験（56週間以上）、4307試験（56週以上）〕中、本剤による治療を受けた320例中71例（22.2%）で抗コンシズマブ抗体の発生が認められた。このうち18例（5.6%）で *in vitro* 中和抗コンシズマブ抗体が陽性であった。*in vitro* 中和抗コンシズマブ抗体が発生した1例において、遊離TFPI濃度がベースライン値まで戻った。

15.1.2 免疫寛容導入療法と本剤を併用した際の安全性及び有効性は確立していない。

16. 薬物動態

16.1 血中濃度

16.1.1 単回投与時

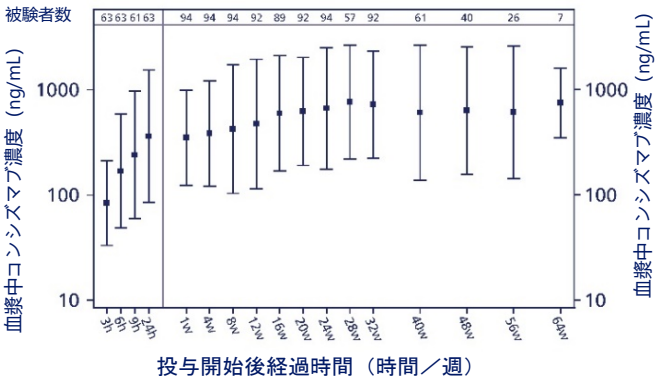
コンシズマブの全身曝露量（C_{max}及びAUC）は、コンシズマブの内皮細胞上のTFPI（標的）への結合とその後の薬物ー標的複合体の消失によって起こる標的介在性の薬物動態（TMDD）により、用量増加に伴い、用量比例性を上回る増加を示した。外国人健康被験者及び血友病A患者ならびに日本人健康被験者（海外在住）を対象に本剤0.05～3mg/kgを単回皮下投与した際の薬物動態パラメータは以下のとおりであった[1),2)]。

	外国人健康被験者（3813試験）			外国人血友病A患者（3813試験）		日本人健康被験者（海外在住）（3981試験）	
投与量	0.05 mg/kg	0.25 mg/kg	1 mg/kg	1 mg/kg	3 mg/kg	0.25 mg/kg	1 mg/kg
例数	3	3	3	3	3	3	3
Cmax (ng/mL)	9.2 (2.5)	36.0 (6.8)	999.0 (427.0)	1791.0 (1588.4)	16689.0 (7079.9)	55.2 (3.9)	276.7 (152.8)
AUC(0-inf) (ng*h/mL)	算出せず	10772.2 (10066.3)	54695.8 (20163.9)	109350.8 (77461.6)	2452323.3 (1275578.8)	7090.8 (689.9)	25426.0 (5916.6)
CL/F (mL/h/kg)	算出せず	37.5 (22.8)	19.9 (6.7)	17.3 (18.0)	1.6 (1.2)	35.6 (3.0)	40.6 (8.5)
tmax (h)	12.0 (8.0, 72.4)	24.1 (12.1, 502.4)	36.0 (24.1, 36.0)	46.5 (34.3, 94.8)	70.4 (47.9, 71.5)	12.1 (8.0, 24.0)	11.8 (8.1, 99.1)
$t_{1/2}$ (h)	算出せず	90.3 (18.2)	114.6 (5.5)	116.7 (69.5)	74.8 (31.5)	96.5 (10.1)	109.9 (16.6)

平均値（標準偏差）〔ただし、tmaxは中央値（最小値,最大値）〕

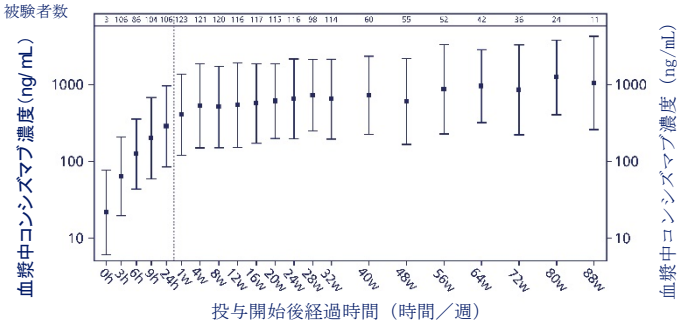
＊16.1.2 反復投与時

日本人及び外国人のインヒビターを保有する血友病A及びB患者に対して、初日に本剤の負荷用量1.0mg/kg/日を投与し、2日目以降0.20mg/kg/日を投与した（最初の5～8週以内に0.25mg/kg/日への増量又は0.15mg/kg/日への減量を可能とした）際の血漿中コンシズマブ濃度の幾何平均の推移は以下のとおりであった。24週時点の血漿中コンシズマブ濃度トラフ値の幾何平均は665.4ng/mL（幾何変動係数：2.2）（N=94例、うち日本人は4例）であった[3)]。



エラーバーは幾何平均の標準偏差を表す。
定量下限値を下回る血漿中濃度については定量下限値の半分の値とした。

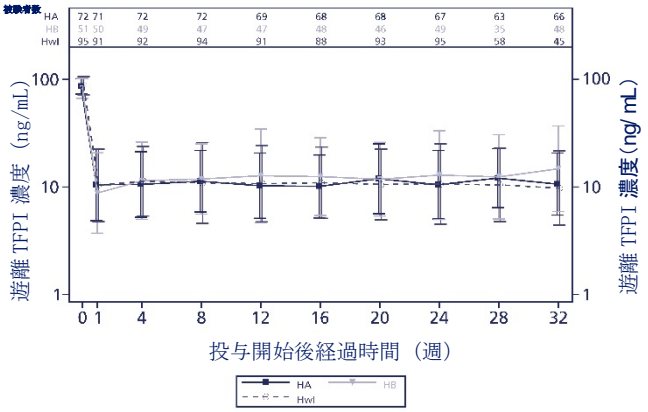
日本人及び外国人のインヒビターを保有しない血友病A及びB患者に対して、初日に本剤の負荷用量1.0mg/kg/日を投与し、2日目以降0.20mg/kg/日を投与した（最初の5～8週以内に0.25mg/kg/日への増量又は0.15mg/kg/日への減量を可能とした）際の血漿中コンシズマブ濃度の幾何平均の推移は以下のとおりであった。24週時点の血漿中コンシズマブ濃度トラフ値の幾何平均は647.3ng/mL〔幾何変動係数：1.8〕（N=116例、うち日本人は9例）であった[4)]。



エラーバーは幾何平均の標準偏差を表す。
定量下限値を下回る血漿中濃度については定量下限値の半分の値とした。

＊ 16.8　その他

日本人及び外国人のインヒビターを保有する、又は保有しない血友病 A 及び B 患者に対して、初日に本剤の負荷用量1.0mg/kg/日を投与し、2日目以降0.20mg/kg/日を投与した（最初の5～8週以内に0.25mg/kg/日への増量又は0.15mg/kg/日への減量を可能とした）際の血漿中 TFPI 濃度の幾何平均の推移は以下のとおりであった（4311 試験[3]及び 4307 試験[4]に基づく）。



HA: インヒビターを保有しない血友病 A, HB: インヒビターを保有しない血友病 B, HwI: インヒビターを保有する血友病 A 及び B
エラーバーは幾何平均の標準偏差を表す。
定量下限値を下回る血漿中濃度については定量下限値の半分の値とした。

17. 臨床成績

17.1　有効性及び安全性に関する試験

17.1.1 国際共同第Ⅲ相臨床試験（4311 試験）

4311 試験は 12 歳以上のインヒビターを保有する血友病 A 及び B 患者 133 例（日本人 7 例を含む）を対象として実施された。本試験は 4 つの治療群で構成され、治療群 1 及び 2（治療群1：バイパス製剤による出血時治療群又は治療群2：本剤定期投与群）において主要な評価を行った。治療群 2 の被験者には初日に負荷投与として 1mg/kg を、2 日目以降 0.20mg/kg/日を投与し、4 週時点の曝露量に基づき 0.25mg/kg/日への増量又は 0.15mg/kg/日への減量を可能とした。治療群 1 及び 2 のすべての被験者が本試験の主要パート（それぞれ 24 及び 32 週）を完了した時点で有効性を評価した。主要パート完了後、治療群 1 の被験者は治療群 2 と同様の投与方法で本剤の投与を開始した。主要評価項目として、治療群 1 及び 2 の治療された出血（自然出血及び外傷性出血）の発現回数について、年換算の出血率を比較した。負の二項回帰モデルを用いた年換算の出血率の推定値、治療群 1 に対する治療群 2 の比を下表に示す[5)6)]。

	治療群 1：出血時治療（19 例）	治療群 2：本剤の定期投与（33 例）
投与期間（週）の中央値（最小値；最大値）	31.1（3.9；72.9）	40.1（3.1；56.3）
治療された自然出血及び外傷性出血		
年換算の出血率（回/年）の中央値（最小値；最大値）	9.8（0.0；94.7）	0.0（0.0；66.4）
年換算の出血率（回/年）の平均値の推定値(95%信頼区間)	11.8（7.03，19.86）	1.7（1.01，2.87）
治療群 1 に対する治療群 2 の年換算の出血率の比(95%信頼区間)	0.14(0.07；0.29)（p<0.001）	

本試験で本剤を投与された全被験者（治療群 1～4）での副作用発現割合は 26.0%（33/127 例）であった。主な副作用は、注射部位反応 17.3%（22/127 例）であった。[5.参照]

＊ 17.1.2　国際共同第Ⅲ相臨床試験（4307 試験）

4307 試験は 12 歳以上のインヒビターを保有しない血友病 A 及び B 患者 156 例（日本人 11 例を含む）を対象として実施された。本試験は 4 つの治療群で構成され、治療群 1 及び 2（治療群1：凝固因子製剤による出血時治療群又は治療群2：本剤定期投与群）において主要な評価を行った。治療群 2 の被験者には初日に負荷投与として 1mg/kg を、2 日目以降 0.20mg/kg/日を投与し、4 週時点の曝露量に基づき 0.25mg/kg/日への増量又は 0.15mg/kg/日への減量を可能とした。治療群 1、2 及び 4 のすべての被験者が本試験の主要パート（それぞれ 24 週、少なくとも 32 週及び少なくとも 32 週）を完了した時点で有効性を評価した。主要パート完了後、治療群 1 の被験者は治療群 2 と同様の投与方法で本剤の投与を開始した。主要評価項目として、治療群 1 及び 2 の治療された出血（自然出血及び外傷性出血）の発現回数について、年換算の出血率を比較した。負の二項回帰モデルを用いた年換算の出血率の推定値、治療群 1 に対する治療群 2 の比を下表に示す[4)]。

	インヒビターを保有しない血友病 A 患者		インヒビターを保有しない血友病 B 患者	
	治療群 1：出血時治療（9 例）	治療群 2：本剤の定期投与（18 例）	治療群 1：出血時治療（12 例）	治療群 2：本剤の定期投与（24 例）
投与期間（週）の中央値（最小値；最大値）	24.1（24.0；36.3）	32.9（21.4；80.4）	24.1（23.6；44.1）	32.3（2.6；80.3）
治療された自然出血及び外傷性出血				
年換算の出血率（回/年）の中央値（最小値；最大値）	19.6（3.3；71.7）	2.9（0.0；29.5）	14.9（0.0；50.9）	1.6（0.0；11.9）
年換算の出血率（回/年）の平均値の推定値（95%信頼区間）	19.3（11.25；33.03）	2.7（1.63；4.59）	14.8（8.14；26.86）	3.1（1.91；5.04）
治療群 1 に対する治療群 2 の年換算の出血率の比（95%信頼区間）	0.14（0.07；0.29）（p<0.001）		0.21（0.10；0.45）（p<0.001）	

本試験で本剤を投与された全被験者（治療群 1～4）での副作用発現割合は 31.1%（47/151 例）であった。主な副作用は、注射部位反応 15.2%（23/151 例）であった。[5.参照]

18. 薬効薬理

18.1　作用機序

コンシズマブは抗組織因子経路インヒビター（抗 TFPI）抗体である。TFPI は活性型血液凝固第 X 因子を阻害する。コンシズマブは TFPI に結合することにより、TFPI による活性型血液凝固第 X 因子の阻害を抑制する。活性型血液凝固第 X 因子活性が増加すると血液凝固の開始期が延長され、効果的な止血に十分な量のトロンビンが生成される。コンシズマブは血液凝固第Ⅷ因子及び第Ⅸ因子とは独立して作用し、コンシズマブの作用は血液凝固第Ⅷ因子又は第Ⅸ因子に対する阻害抗体の有無の影響を受けない。

コンシズマブは血液凝固第Ⅷ因子又は第Ⅸ因子との構造相関性あるいは配列相同性が認められないことから、血液凝固第Ⅷ因子又は第Ⅸ因子に対するインヒビターの生成を誘発又は増強しない。

18.2　*In vitro* トロンビン生成改善作用

コンシズマブは血友病 A（インヒビターの有無に関わらず）及び血友病 B（インヒビター無）患者から得られた血漿において、トロンビン生成を改善した[7)]。

18.3　全血を用いた *in vitro* 止血栓形成改善作用

コンシズマブは、正常血液にそれぞれ抗血液凝固第Ⅷ因子抗体と抗血液凝固第Ⅸ因子抗体を添加することによって模倣されたヒト血友病 A 様又は血友病 B 様状態の全血に対し、止血栓形成を改善した[8)]。

18.4　*In vivo* 止血作用

コンシズマブは抗体誘発血友病 A ウサギの爪上皮出血モデルに対し、出血量を減少させた[9),10)]。

19. 有効成分に関する理化学的知見

一般名：コンシズマブ（遺伝子組換え）　(JAN)
Concizumab (Genetical Recombination)　(JAN)

分子式：$C_{6462}H_{10004}N_{1712}O_{2046}S_{46}$

分子量：約 149,000

本　質：448 個のアミノ酸残基からなる H 鎖（γ4 鎖）2 本及び 219 個のアミノ酸残基からなる L 鎖（κ鎖）2 本で構成される糖タンパク質

20. 取扱い上の注意

凍結を避けること。また、熱及び光を避けて保管し、直射日光下での保管は避けること。

21. 承認条件

21.1　医薬品リスク管理計画を策定の上、適切に実施すること。

〈血液凝固第Ⅷ因子又は第Ⅸ因子に対するインヒビターを保有する先天性血友病患者における出血傾向の抑制〉

21.2　日本人での投与経験が極めて限られていることから、製造販売後、一定数の症例に係るデータが集積されるまでの間は、全症例を対象に使用成績調査を実施することにより、本剤の使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを早期に収集し、本剤の適正使用に必要な措置を講じること。

22. 包装

〈15mg〉
1.5mL×1 本
〈60mg〉
1.5mL×1 本
〈150mg〉
1.5mL×1 本
〈300mg〉
3mL×1 本

23. 主要文献

1)　社内資料：第Ⅰ相臨床試験（NN7415-3813 試験）
2)　社内資料：第Ⅰ相臨床試験（NN7415-3981 試験）
3)　社内資料：第Ⅲ相臨床試験（NN7415-4311 試験）
（2023 年 9 月 25 日承認 CTD2.7.2.3）
4)　社内資料：第Ⅲ相臨床試験（NN7415-4307 試験）
5)　社内資料：第Ⅲ相臨床試験（NN7415-4311 試験）
6)　Matsushita T., et al.： N Engl J Med. 2023;389(9):783-94
7)　Waters EK., et al.: Haemophilia. 2017;23(5):769-76
8)　社内資料（2023 年 9 月 25 日承認 CTD2.6.2.2）
9)　Hilden I., et al.: Blood. 2012;119(24):5871-8
10)　Lauritzen B., et al.: Haemophilia. 2019;25(6):e379-82

24. 文献請求先及び問い合わせ先

ノボ ノルディスク ファーマ株式会社　ノボケア相談室
〒100-0005　東京都千代田区丸の内 2-1-1
Tel 0120-180363（フリーダイアル）

26. 製造販売業者等

26.1　製造販売元

ノボ ノルディスク ファーマ株式会社
東京都千代田区丸の内 2－1－1
www.novonordisk.co.jp

アレモ®及び Alhemo®は Novo Nordisk Health Care AG の登録商標です。ペンニードル®は Novo Nordisk A/S の登録商標です。

＊添付文書（案）は審査段階のものであり、最新の添付文書を参照すること。

日本標準商品分類番号
876349

貯　　法：2～8℃で保存
有効期間：2年

生物由来製品、処方箋医薬品注）

抗 TFPI モノクローナル抗体
マルスタシマブ（遺伝子組換え）

ヒムペブジ®皮下注150mgペン

HYMPAVZI® S.C. Injection 150mg Pen

注）注意-医師等の処方箋により使用すること

承認番号	30600AMX00302
販売開始	2025年3月

1. 警告

1.1 本剤の臨床試験において、重篤な血栓塞栓性事象の発現が複数例に認められている。本剤投与中は観察を十分に行い、血栓塞栓性事象が疑われる場合には本剤の投与を中止し、適切な処置を行うこと。また、患者に対し、血栓塞栓性事象の兆候や症状について十分説明すること。[8.1、9.1.1、9.1.2、11.1.1、15.2.1、15.2.2参照]

1.2 本剤は、血友病治療に十分な知識・経験を持つ医師のもと、緊急時に十分対応できる医療機関で投与開始すること。[8.1、9.1.1、9.1.2、11.1.1参照]

1.3 本剤の投与開始に先立ち、患者又は介護者に危険性を十分説明し、同意を得た上で本剤を投与すること。

2. 禁忌（次の患者には投与しないこと）

本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

容量	1筒中 1mL	
有効成分	マルスタシマブ（遺伝子組換え） 150mg	
添加剤	L-ヒスチジン	1.12mg
	L-ヒスチジン塩酸塩水和物	2.67mg
	精製白糖	85mg
	エデト酸ナトリウム水和物	0.05mg
	ポリソルベート80	0.2mg

本剤は、チャイニーズハムスター卵巣細胞を用いて製造される。

3.2 製剤の性状

性状	無色～淡黄色澄明の液
pH	5.3～6.3
浸透圧比	約1.2（生理食塩液に対する比）
形態	固定注射針付きシリンジを注入器にセットしたコンビネーション製品

4. 効能又は効果

先天性血友病患者における出血傾向の抑制

5. 効能又は効果に関連する注意

本剤は、血液凝固第Ⅷ因子又は第Ⅸ因子に対するインヒビターの有無によらず有効性が確認されている。[17.1.1-17.1.3 参照]

6. 用法及び用量

通常、12歳以上かつ体重25kg以上の患者には、マルスタシマブ（遺伝子組換え）として初回に300mgを皮下投与し、以降は1週間隔で1回150mgを皮下投与する。なお、体重50kg以上で効果不十分な場合には、1週間隔で1回300mgに増量して皮下投与できる。

7. 用法及び用量に関連する注意

7.1 本剤は、出血傾向の抑制を目的とした定期的な投与のみに使用し、出血時の止血を目的とした投与は行わないこと。[8.4.3参照]

7.2 本剤の投与にあたっては投与忘れがないよう十分指導すること。投与予定日に本剤を投与できなかった場合は、可能な限り速やかに予定していた用量で投与を再開し、以降は原則としてその投与日を起点として週1回投与すること。なお、投与再開日が最終投与日から14日目以降の場合、再開時の初回投与量は300mgとすること。

8. 重要な基本的注意

8.1 本剤の臨床試験において、重篤な血栓塞栓性事象の発現が認められている。血栓塞栓性事象があらわれる可能性があるので、血栓塞栓性事象の既往又は危険因子の有無を慎重に確認した上で、本剤の投与を開始すること。また、患者に対し、血栓塞栓性事象の兆候や症状について十分説明するとともに、以下の注意事項の重要性についても理解を得た上で投与を開始すること。[1.1、1.2、9.1.1、9.1.2、11.1.1、15.2.1、15.2.2参照]

8.2 バイパス止血製剤（活性型第Ⅶ因子製剤、活性型プロトロンビン複合体製剤、乾燥濃縮人血液凝固第Ⅹ因子加活性化第Ⅶ因子製剤）、血液凝固第Ⅷ因子又は第Ⅸ因子製剤による補充療法から本剤に切り替える場合は、切り替え前の製剤の半減期を考慮し、本剤投与開始前の適切な時期に中止すること。[15.2.2参照]

8.3 バイパス止血製剤又は血液凝固因子製剤以外の血友病治療薬から本剤に切り替える場合の指針となる臨床試験データは得られていない。バイパス止血製剤又は血液凝固因子製剤以外の血友病治療薬から本剤に切り替える場合は、その製剤の半減期に基づき適切な休薬期間（少なくとも半減期の5倍の期間）の設定を考慮するなどし、本剤の投与を開始すること。休薬期間中は、必要に応じてバイパス止血製剤又は血液凝固因子製剤による補充療法を行うこと。

8.4 本剤による治療期間中に出血が発現した場合は、以下の点に注意すること。

8.4.1 必要に応じてバイパス止血製剤、血液凝固第Ⅷ因子又は第Ⅸ因子製剤の投与を行うこと。その場合は本剤との併用投与が可能であるが、各製剤の電子添文や最新のガイドラインに従って投与し、投与量は、承認されている最低用量を目安として出血部位や程度に応じて判断すること。さらに、以下の点にも注意すること。[15.2.2参照]

(1) 活性型第Ⅶ因子製剤については、承認されている用法・用量の範囲内で使用し、初回投与量は90μg/kg、その後は約2時間ごとを超えない投与頻度で1回投与量として60～90μg/kgを投与することが望ましい。

(2) 活性型プロトロンビン複合体製剤については、24時間以内の最高用量は100単位/kgを上限とすることが望ましい。

8.4.2 バイパス止血製剤、血液凝固第Ⅷ因子又は第Ⅸ因子製剤の自己注射が必要になった場合に備え、バイパス止血製剤又は血液凝固因子製剤の投与間隔及び投与量について患者又は介護者に説明すること。

8.4.3 止血を目的とした本剤の追加投与及び用量変更は行わないこと。[7.1参照]

8.4.4 血液凝固系検査等により患者の状態を注意深く観察し、異常が認められた場合は本剤の投与を中止し適切な処置を行うこと。

8.5 大手術時における本剤の有効性及び安全性は確立されていないため、大手術を行う場合は、本剤の投与を中止し、バイパス止血製剤又は血液凝固因子製剤を用いた標準治療を行い、周術期における静脈血栓症発現のリスクを管理すること。本剤の投与を再開する場合は、術後の血栓塞栓症リスク因子の有無や、その他の止血製剤及び併用薬の使用等、患者の全身状態を考慮すること。なお、抜歯等の小手術では本剤の用量変更又は投与中止の必要はない。

8.6 本剤による治療中の患者において、過敏症反応の可能性がある発疹及びそう痒症の皮膚症状が報告されている。重度の過敏症反応が認められた場合には、本剤の投与を中止し、速やかに適切な処置を行うこと。[11.1.2参照]

8.7 自己注射にあたっては、投与法について十分な教育訓練を実施したのち、患者又は介護者が確実に投与できることを確認した上で、医師の管理指導の下で実施すること。また、患者又は介護者に対し、自己注射後に何らかの異常が認められた場合は、速やかに医療機関へ連絡するよう指導すること。適用後、自己注射の継続が困難な状況となる可能性がある場合には、医師の管理の下で慎重に観察するなど、適切な対応を行うこと。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 血栓塞栓性事象の既往又は危険因子を有する患者

本剤投与により血栓塞栓性事象のリスクが高まる可能性がある。投与に際しては有益性と危険性を十分考慮すること。[1.1、1.2、8.1、11.1.1、15.2.1、15.2.2参照]

9.1.2 組織因子が過剰に発現している状態にある患者

組織因子が過剰に発現している状態（進行したアテローム性疾患、癌、挫滅、敗血症、炎症病態等）では、本剤投与により血栓塞栓性事象又は播種性血管内凝固症候群（DIC）のリスクが高まる可能性がある。[1.1、1.2、8.1、11.1.1、15.2.1、15.2.2参照]

9.4 生殖能を有する者

妊娠する可能性のある女性には、本剤投与中及び最終投与後1ヵ月間において避妊する必要性及び適切な避妊法について説明すること。

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。ラットの胚・胎児発生に関する試験において、最大臨床用量（本剤300mgを週1回皮下投与）におけるAUCの4.3倍に相当する用量で影響は認められなかったが、17倍に相当する用量で胚・胎児毒性（骨格奇形及び骨格変異並びに着床後胚損失の増加）が認められた。一方、ウサギの胚・胎児発生に関する試験では、最大臨床用量（本剤300mgを週1回皮下投与）におけるAUCの32倍に相当する用量で影響は認められなかった。また、一般にヒトIgGは胎盤を通過することが知られており、本剤を妊婦に投与した場合、胎児及び出生児における血栓形成リスクが否定できない。[15.2.1、15.2.2参照]

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤のヒト乳汁中への移行性は不明であるが、一般にヒトIgGはヒト乳汁中に移行することが知られている。

9.7 小児等

12歳未満の小児を対象とした臨床試験は実施していない。

9.8 高齢者

患者の状態を観察しながら慎重に投与すること。一般に、生理機能が低下していることが多い。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 血栓塞栓性事象（0.6%）

[1.1、1.2、8.1、9.1.1、9.1.2、15.2.1、15.2.2参照]

11.1.2 ショック、アナフィラキシー（いずれも頻度不明）

発疹、そう痒、呼吸困難、喘鳴、血圧低下等の症状が認められた場合には投与を中止し、適切な処置を行うこと。[8.6参照]

11.2 その他の副作用

	3%以上	3%未満
感染症および寄生虫症		丹毒
血液およびリンパ系障害		好中球減少症
神経系障害		頭痛、浮動性めまい
胃腸障害		痔核、腹痛
皮膚および皮下組織障害		発疹、そう痒症
筋骨格系および結合組織障害		関節痛、出血性関節症
先天性、家族性および遺伝性障害		リンパ管奇形
一般・全身障害および投与部位の状態	注射部位反応（紅斑、そう痒感、腫脹、出血、浮腫、硬結、疼痛等）（11.4%）	疲労、末梢腫脹
臨床検査	フィブリンDダイマー増加、プロトロンビンフラグメント1・2増加	アラニンアミノトランスフェラーゼ増加
傷害、中毒および処置合併症		挫傷

14. 適用上の注意

14.1 薬剤投与前の注意

14.1.1 冷蔵庫から取り出し、直射日光を避け、外箱に入れたまま15～30分間かけて室温（30℃以下）に戻しておくこと。その他の方法（電子レンジや熱湯等）を用いて本剤を温めないこと。

14.1.2 一度室温（30℃以下）に戻した薬剤は、再び冷蔵庫に戻さないこと。

14.1.3 本剤を室温(30℃以下)に戻した後は7日以内に使用すること。7日以内に使用しなかった場合は適切に廃棄すること。

14.1.4 本剤を振とうしないこと。

14.1.5 本剤は無色～淡黄色澄明の液である。内容物を目視により確認し、異物又は変色（濁りや暗黄色）等を認めた場合には使用しないこと。

14.2 薬剤投与時の注意

14.2.1 他の医薬品と本剤を混合しないこと。

14.2.2 投与部位は腹部又は大腿部とすること。

14.2.3 投与ごとに投与部位を変えることが望ましい。骨ばった部位や内出血、発赤、圧痛、硬結、瘢痕又は創傷等が認められる部位には投与しないこと。

14.2.4 300mgの投与を行う場合は、150mgの注射をそれぞれ異なる部位に投与すること。

14.2.5 本剤による治療期間中に他の製剤の皮下投与を行う場合は、異なる部位に投与することが望ましい。

14.2.6 静脈内への投与は行わないこと。

14.2.7 本剤は1回使い切りである。保存剤を含有していないため、未使用残液は適切に廃棄すること。

14.3 薬剤交付時の注意

14.3.1 保管方法について適切に指導すること。[20.1、20.2参照]

14.3.2 投与の際は必ず取扱説明書を参照するよう指導すること。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 血友病A又は血友病B患者を対象とした国際共同第Ⅲ相臨床試験（B7841005試験）及びB7841005試験を完了した患者を対象とした国際共同第Ⅲ相臨床試験（B7841007試験）の併合解析において、抗薬物抗体（ADA）の評価が可能な167例中39例（23.4%）でADAの発現が認められ、インヒビター非保有患者では23.3%（27/116例）、インヒビター保有患者では23.5%（12/51例）であった。ADA発現例のうち66.7%（26/39例）は一過性、30.8%（12/39例）は持続性であり、97.4%（38/39例）はデータカットオフ時までに消失した。ADA発現例における中和抗体（NAb）の発現割合は20.5%（8/39例）であり、インヒビター非保有患者では22.2%（6/27例）、インヒビター保有患者では16.7%（2/12例）であった。認められたNAbの大部分（87.5%）は一過性で、NAbはデータカットオフ時までに消失した。B7841005試験の12ヵ月間の本剤投与期間において、ADAの発現が認められた患者ではADAの発現が認められなかった患者と比較して、本剤の平均血漿中濃度に低下傾向（約10%～36%）が認められたが、ADA及びNAbの発現による本剤の有効性及び安全性に対する影響を示唆する成績は得られていない[1)]。[17.1.1-17.1.3参照]

15.1.2 免疫寛容導入療法と本剤を併用した際の安全性及び有効性は確立していない。

15.2 非臨床試験に基づく情報

15.2.1 ラットを用いたマルスタシマブの6ヵ月間反復投与毒性試験において、最大臨床用量（本剤300mgを週1回皮下投与）におけるAUCの7.6倍に相当する用量から血栓形成が認められ、血栓形成に対する無影響量及び安全域は得られていない。[1.1、8.1、9.1.1、9.1.2、9.5、11.1.1参照]

15.2.2 ラットを用いた試験において、最大臨床用量（本剤300mgを週1回皮下投与）におけるC_{max}の27倍に相当する用量のマルスタシマブと最大臨床用量（270μg/kg）を投与した時の定常状態でのC_{max}を上回るよう設定した用量（3mg/kg）の活性型血液凝固第Ⅶ因子製剤を併用投与した結果、単独投与と比較して肺及び投与部位での血栓・塞栓の発現頻度の増加及び重症度の悪化が認められた。一方、27倍（C_{max}比較）に相当する用量のマルスタシマブと0.8mg/kgの活性型血液凝固第Ⅶ因子製剤の併用投与、3倍（C_{max}比較）に相当する用量のマルスタシマブと臨床用量（100U/kg/日）と同用量の活性型プロトロンビン複合体製剤の併用投与、及び2倍（C_{max}比較）に相当するマルスタシマブと出血時の最大臨床用量（活性化人血液凝固第Ⅶ因子として180μg/kg/日）と同用量の乾燥濃縮人血液凝固第Ⅹ因子加活性化第Ⅶ因子製剤の併用投与では、単独投与と比較して明確な影響は認められなかった[2]。[1.1、8.1、8.2、8.4.1、9.1.1、9.1.2、9.5、11.1.1参照]

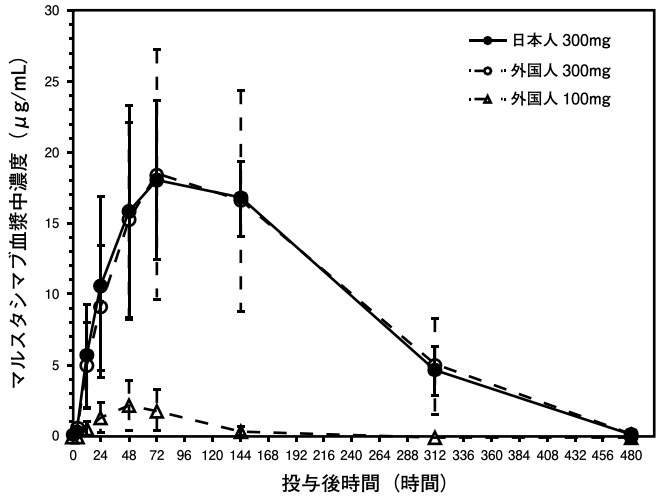
16. 薬物動態

16.1 血中濃度

16.1.1 単回投与

日本人又は外国人健康成人男性16例に本剤100又は300mgを単回皮下投与したときのマルスタシマブの血漿中濃度推移及び薬物動態パラメータを以下に示す[3]。

健康成人に単回皮下投与したときのマルスタシマブの血漿中濃度推移（平均値±標準偏差）



健康成人に100又は300mgを単回皮下投与したときのマルスタシマブの薬物動態パラメータ

	投与量（mg）	例数	C_{max}（μg/mL）	AUC_{last}（μg・h/mL）	AUC_{inf}（μg・h/mL）	T_{max}（h）	$t_{1/2}$（h）
外国人	100	6[a)]	1.18（287）	81.89（391）	257.7（34）	48（48.0-72.0）	33.3±5.4
	300	6[b)]	16.49（63）	3120（68）	2799（83）	72（48.0-144）	65.8±18.0
日本人	300	4[c)]	18.5（25）	3551（28）	4240，5670	108（72.0-144）	74.7，122

C_{max}、AUC_{last}及びAUC_{inf}は幾何平均値（幾何変動係数%）、T_{max}は中央値（最小値-最大値）、$t_{1/2}$は平均値±標準偏差、2例以下は個別値

a）AUC_{inf}及び$t_{1/2}$は4例、b）AUC_{inf}及び$t_{1/2}$は3例、c）AUC_{inf}及び$t_{1/2}$は2例

16.1.2 反復投与

体重25kg以上の成人（18歳以上）及び青年（12～18歳未満）のインヒビター非保有及び保有血友病A又は血友病B患者に初回に本剤300mgを皮下投与し、以降は150mgを週1回皮下投与したときの$C_{min,ss}$、$C_{max,ss}$及びAUC_{ss}の母集団薬物動態解析[注1)]に基づく推定値を以下に示す。定常状態時の累積係数の幾何平均値は約4～5であった。本剤投与後の血漿中濃度は、初回投与から約60日後、すなわち8回目又は9回目の皮下投与までに定常状態に達すると考えられる[4]。

成人及び青年のインヒビター非保有及び保有血友病患者に初回に300mgを皮下投与し、以降は150mg週1回で反復皮下投与したときの定常状態時のマルスタシマブの母集団薬物動態パラメータ

薬物動態パラメータ	成人		青年	
インヒビター	非保有	保有	非保有	保有
例数	99	34	29	21
$C_{min,ss}$（μg/mL）	7.01（236）	8.44（253）	23.2（87.7）	27.0（79.1）
$C_{max,ss}$（μg/mL）	12.5（121）	15.2（125）	31.1（70.2）	36.9（63.6）
AUC_{ss}（μg・h/mL）	1790（140）	2170（144）	4760（74.7）	5610（67.6）

$C_{min,ss}$：定常状態時の最小血漿中濃度、$C_{max,ss}$：定常状態時の最高血漿中濃度、AUC_{ss}：定常状態時の血漿中濃度-時間曲線下面積

値はすべて幾何平均値（幾何変動係数%）

16.2 吸収

18歳以上65歳未満のインヒビター非保有及び保有血友病A又は血友病B患者20例に本剤150～450mgを週1回反復皮下投与[注2)]したときのT_{max}の中央値は23～59時間であった（外国人データ）[5]。母集団薬物動態解析[注1)]の結果から、皮下投与後のマルスタシマブのバイオアベイラビリティは約72%と推定され、投与部位（腕、大腿部、腹部）による差異は見られなかった[6]。

16.3 分布

インヒビター非保有及び保有血友病患者における定常状態時のマルスタシマブの分布容積は、母集団薬物動態解析[注1)]の結果から6.2Lであり[7]、血管外への分布は限定的であると考えられる。

注1）健康成人、成人及び青年のインヒビター非保有及び保有血友病A又は血友病B患者287例から得られた血漿中マルスタシマブ濃度及び総TFPI濃度を用いて母集団薬物動態解析を実施した。

注2）本剤の承認された用量は、初回に300mg、以降は1週間隔で1回150mgである。

17. 臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 国際共同第Ⅲ相臨床試験（B7841005試験、インヒビター非保有コホート）（jRCT2080225164）

成人及び青年（男性、12歳以上75歳未満、体重35kg以上）のインヒビター非保有の重症血友病A又は中等症～重症[注)]血友病B患者を対象とし、6ヵ月間の観察期間後に、本剤を初回に300mg皮下投与し、以降は1週間隔で1回150mgを皮下投与した。用量増量基準（体重50kg以上等）を満たした患者は、本剤投与6ヵ月後以降に300mg週1回皮下投与に増量可とした。観察期間における治療は血液凝固第Ⅷ因子又は第Ⅸ因子製剤による出血時補充療法又は定期補充療法とした。

主要評価項目は治療を要した出血の年換算出血率とし、6ヵ月間の観察期間と12ヵ月間の本剤投与期間の治療を要した出血の年換算出血率を比較した。観察期間に出血時補充療法を受けた33例（外国人データ）の成績は下表のとおりであり、年換算出血率の比（本剤投与期間/観察期間）の95%信頼区間の上限値は、事前に設定された評価基準である0.5を下回った。

注）血液凝固第Ⅸ因子の活性値が2%以下

	観察期間（33例） 6ヵ月間の血液凝固因子製剤による出血時補充療法	本剤投与期間（33例） 12ヵ月間の本剤定期投与
年換算出血率の最小二乗平均値[a)]［95%信頼区間］（回/年）	39.86［33.05，48.07］	3.20［2.10，4.88］
年換算出血率（最小二乗平均値[a)]）の比（本剤投与期間/観察期間）［95%信頼区間］、p値[b)]	0.080 ［0.057，0.113］、<0.0001	

a）出血回数に負の二項分布を仮定して、リンク関数をlogとし、治療群を因子、観察期間（対数年）をオフセット項とした一般化推定方程式（分散共分散構造は無構造）

b）年換算出血率の比=0.5を帰無仮説とした両側検定、有意水準5%

観察期間に定期補充療法を受けた83例（日本人患者4例を含む）の成績は下表のとおりであった。

	観察期間（83例） 6ヵ月間の血液凝固因子製剤による定期補充療法	本剤投与期間（83例） 12ヵ月間の本剤定期投与
年換算出血率の最小二乗平均値[a] ［95%信頼区間］（回/年）	7.90［5.14，10.66］	5.09［3.40，6.78］
年換算出血率（最小二乗平均値[a]）の差（本剤投与期間－観察期間） ［95%信頼区間］（回/年）	－2.81 ［－5.42，－0.20］	

a）出血回数に負の二項分布を仮定して、リンク関数をidentityとし、観察期間（年）、観察期間（年）と治療群の交互作用を因子、切片なしとした一般化推定方程式（分散共分散構造は無構造）

本剤が投与された全患者での因果関係を否定できない有害事象の発現頻度は19.8%（23/116例）であり、主なものは注射部位そう痒感、そう痒症が各3.4%（4/116例）、注射部位紅斑、プロトロンビンフラグメント1・2増加が各2.6%（3/116例）、注射部位疼痛、注射部位腫脹、フィブリンDダイマー増加が各1.7%（2/116例）であった[8]。［5.、15.1.1参照］

17.1.2 国際共同第Ⅲ相臨床試験（B7841005試験、インヒビター保有コホート）（jRCT2080225164）

成人及び青年（男性、12歳以上75歳未満）のインヒビター保有の重症血友病A又は中等症～重症[注)]血友病B患者を対象とし、6ヵ月間の観察期間後に、本剤を初回に300mg皮下投与し、以降は1週間隔で1回150mgを皮下投与した。用量増量基準（体重50kg以上等）を満たした患者は、本剤投与6ヵ月後以降に300mg週1回皮下投与に増量可とした。観察期間における治療はバイパス止血製剤による出血時補充療法又は定期補充療法とした。

主要評価項目は治療を要した出血の年換算出血率とし、6ヵ月間の観察期間と12ヵ月間の本剤投与期間の治療を要した出血の年換算出血率を比較した。観察期間に出血時補充療法を受けた48例（外国人データ）の成績は下表のとおりであり、年換算出血率の比（本剤投与期間/観察期間）の95%信頼区間の上限値は、事前に設定された評価基準である0.5を下回った。

注）血液凝固第Ⅸ因子の活性値が2%以下

	観察期間（48例） 6ヵ月間のバイパス止血製剤による出血時補充療法	本剤投与期間（48例） 12ヵ月間の本剤定期投与
年換算出血率の最小二乗平均値[a] ［95%信頼区間］（回/年）	19.78［16.12，24.27］	1.39［0.85，2.29］
年換算出血率（最小二乗平均値[a]）の比（本剤投与期間/観察期間） ［95%信頼区間］、p値[b]	0.070 ［0.042，0.118］、<0.0001	

a）出血回数に負の二項分布を仮定して、リンク関数をlogとし、治療群を因子、観察期間（対数年）をオフセット項とした一般化推定方程式（分散共分散構造は無構造）

b）年換算出血率の比=0.5を帰無仮説とした両側検定、有意水準5%

観察期間にバイパス止血製剤による定期補充療法を受けた3例（日本人患者1例を含む）では、治療を要した出血の年換算出血率の平均値（標準偏差）は、観察期間で7.61（2.95）、本剤投与期間で1.03（1.02）であった。

本剤が投与された全患者での因果関係を否定できない有害事象の発現頻度は31.4%（16/51例）であり、主なものはフィブリンDダイマー増加が9.8%（5/51例）、プロトロンビンフラグメント1・2増加が5.9%（3/51例）、注射部位紅斑、注射部位疼痛、注射部位腫脹、アラニンアミノトランスフェラーゼ増加、発疹が各3.9%（2/51例）であった[9]。［5.、15.1.1参照］

17.1.3 国際共同第Ⅲ相臨床試験（B7841007試験）（jRCT2041220046）

B7841005試験を完了した成人及び青年のインヒビター保有又は非保有の男性血友病A又は血友病Bの患者を対象とし、本剤を定期投与したときの長期の安全性及び忍容性を主要目的として評価する実施中の非盲検延長試験である。

本剤を投与された全患者での投与期間の中央値は903日、因果関係を否定できない有害事象の発現頻度は7.1%（11/154例）であり、主なものは注射部位内出血が1.9%（3/154例）、注射部位腫脹、発疹が各1.3%（2/154例）であった（データカットオフ：2025年5月）[10]。［5.、15.1.1参照］

18. 薬効薬理

18.1 作用機序

マルスタシマブは外因系凝固経路を阻害する組織因子経路インヒビター（TFPI）のKunitzドメイン2（K2）を標的とするヒトモノクローナルIgG1抗体である。TFPIはK2を介して活性型血液凝固第Ⅹ因子の活性部位に結合し、これを阻害する[11]。マルスタシマブは、TFPIによる活性型血液凝固第Ⅹ因子の阻害を抑制することにより外因系凝固経路を増強する。

18.2 *In vitro*抗原結合及び血液凝固第Ⅹ因子活性化作用

マルスタシマブは、プラズモン共鳴法による*in vitro*タンパク質結合測定系においてヒトTFPI K2及びTFPI K1K2に結合したが、ヒトTFPI K1への結合はみられなかった[12]。また、酵素発色法による*in vitro*酵素反応測定系において、マルスタシマブは、TFPIによる活性型血液凝固第Ⅹ因子の阻害活性を抑制した[13]。

18.3 *In vitro*止血作用

マルスタシマブは、インヒビター保有患者を含む血友病A患者及び血友病B患者から採取した血漿のいずれにおいても、*in vitro*添加により希釈プロトロンビン時間の短縮及びトロンビン生成の増加を示し、止血作用を示した[14]。

18.4 *In vivo*止血作用

雄の血友病A（血液凝固第Ⅷ因子欠損）及び血友病B（血液凝固第Ⅸ因子欠損）モデルマウスを用いた重度の尾部出血モデルにおいて、マルスタシマブ投与による出血量の減少がみられた[15]。

19. 有効成分に関する理化学的知見

一般的名称：マルスタシマブ（遺伝子組換え）
Marstacimab（Genetical Recombination）（JAN）

本質：マルスタシマブは、遺伝子組換え抗組織因子経路インヒビター（TFPI）モノクローナル抗体であり、ヒトIgG1に由来する。H鎖の3つのアミノ酸残基が置換（L237A、L238A、G240A）され、C末端のK450は除去されている。マルスタシマブは、CHO細胞により産生される。マルスタシマブは、449個のアミノ酸残基からなるH鎖（γ1鎖）2本及び218個のアミノ酸残基からなるL鎖（λ鎖）2本で構成される糖タンパク質（分子量：約146,000）である。

20. 取扱い上の注意

20.1 光を避けるため、本剤は外箱に入れて保存すること。［14.3.1参照］

20.2 凍結を避けること。［14.3.1参照］

21. 承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。

21.2 製造販売後、一定数の症例に係るデータが集積されるまでの間は、全症例を対象に使用成績調査を実施すること。

22. 包装

1mL×1本

23. 主要文献

1) 免疫原性（xxxx年xx月xx日承認、CTD2.7.2.3.2.9、CTD2.7.2.2.2.3.2）
2) 効力を裏付ける薬理試験（2024年12月27日承認、CTD2.6.2.2.2.2）
3) B7841001試験：単回投与後の薬物動態（2024年12月27日承認、CTD2.7.2.2.1.1）
4) 反復投与後の薬物動態（xxxx年xx月xx日承認、CTD2.7.2.3.1.3）
5) 吸収（2024年12月27日承認、CTD2.7.2.3.1.1.1）
6) バイオアベイラビリティ（2024年12月27日承認、CTD2.7.2.3.3.3）
7) 分布（xxxx年xx月xx日承認、CTD2.7.2.3.1.1.2）

8) B7841005試験（2024年12月27日承認、CTD2.7.3.2.3、CTD2.7.4.2.1.1.3）
9) B7841005試験（xxxx年xx月xx日承認、CTD2.7.3.2.2.1、CTD2.7.4.2.1.1.3.1）
10) 社内資料：B7841007試験
11) Broze GJ Jr, Girard TJ. Tissue factor pathway inhibitor: structure-function. Front Biosci (Landmark Ed) 2012；17：262-80.
12) 効力を裏付ける薬理試験（2024年12月27日承認、CTD2.6.2.2.1.2）
13) 効力を裏付ける薬理試験（2024年12月27日承認、CTD2.6.2.2.1.3）
14) 効力を裏付ける薬理試験（2024年12月27日承認、CTD2.6.2.2.1.6）
15) 効力を裏付ける薬理試験（2024年12月27日承認、CTD2.6.2.2.2.1）

24. 文献請求先及び問い合わせ先

ファイザー株式会社
Pfizer Connect/メディカル・インフォメーション
〒151-8589　東京都渋谷区代々木3-22-7
TEL　0120-664-467

26. 製造販売業者等

26.1 製造販売元

ファイザー株式会社
東京都渋谷区代々木3-22-7

Ⓡ登録商標

1. 効能又は効果（案）とその設定根拠

1.1. 効能又は効果（案）（取り消し線箇所を削除）

~~血液凝固第VIII因子又は第IX因子に対するインヒビターを保有しない~~先天性血友病患者における出血傾向の抑制

以下に示す臨床試験の結果に基づき、現在承認が得られている効能又は効果（「血液凝固第 VIII 因子又は第 IX 因子に対するインヒビターを保有しない先天性血友病患者における出血傾向の抑制」）に「血液凝固第 VIII 因子又は第 IX 因子に対するインヒビターを保有する先天性血友病患者における出血傾向の抑制」の適応を追加した。

1.2. 効能又は効果（案）の設定根拠

1.2.1. 有効性

第 3 相検証的試験である B7841005 試験において、インヒビター保有の 12 歳以上の重症の血友病 A 又は中等度重症から重症の血友病 B の治験参加者を対象として、主要評価項目である治療を要した出血の ABR、重要な副次評価項目、その他の重要な健康関連 QoL 評価項目について、バイパス製剤による出血時補充療法と比較した場合のマルスタシマブ定期投与の有効性が示された。

B7841005 試験の治療を要した出血の ABR から、観察期間中のバイパス製剤による出血時補充療法に対するマルスタシマブ定期投与の優越性が検証された（両側 p 値<0.0001）。モデルに基づく平均 ABR は、投与期のマルスタシマブの定期投与で 1.39（95% CI: 0.85, 2.29）、観察期の出血時補充療法で 19.78（95% CI: 16.12, 24.27）であり、出血時補充療法に対するマルスタシマブ定期投与の ABR 比は 0.070（95% CI: 0.042, 0.118）、ABR 低下率は 93%であった（M2.7.3.1.2.1）。

実施中の第 3 相非盲検長期継続投与試験である B7841007 試験では、マルスタシマブの定期投与の有効性（治療を要した出血の ABR）の維持が示された。B7841007 試験でのマルスタシマブの投与期間は、B7841005 試験での 12 カ月間を超えて、最長 1240 日間（約 41 カ月間）［中央値：616.0 日間（20.5 カ月間）、範囲：34～1240 日間（1.1～41.3 カ月間）］[a]であった。

マルスタシマブ定期投与期間中の出血コントロールは、部分集団間（血友病型、年齢、人種、地理的地域など）で一貫して認められ、これらの部分集団間で認められたマルスタシマブの治療効果は主要解析の結果と一致していた。マルスタシマブは、観察期間中の ABR の範囲及びベースラインの標的関節数によらず、一貫して低下した ABR を示した。すべての部分集団を通して、B7841007 試験で長期継続投与に伴う ABR の低下傾向が認められた。

全体として、マルスタシマブの定期投与により、12 歳以上のインヒビター保有の血友病 A 又は血友病 B の治験参加者における重大な出血の転帰の改善が認められ、この結果は初回申請時に

[a] 期間（月）は 1 カ月間を 30 日間として換算した値を示す。

12 歳以上のインヒビター非保有の治験参加者に対して認められたマルスタシマブの有効性の結果とも整合していた。

詳細は M2.5.4.1 を参照。

1.2.2. 安全性

マルスタシマブは、12 歳以上のインヒビター保有の血友病 A 又は血友病 B の治験参加者に対し、出血事象の予防のための定期投与として、初回負荷投与で 300 mg 皮下投与後に 150 mg 週 1 回皮下投与したとき、おおむね安全で忍容性も良好であった。

また、初回承認申請時のインヒビター非保有の治験参加者のデータと比較して、新たな安全性上の懸念は認められなかった。本一変申請におけるマルスタシマブの安全性プロファイルは、12 歳以上のインヒビター非保有の治験参加者における初回承認申請データとおおむね同様であった。

血友病型、人種、民族又は地理的地域別に解析した結果、有害事象、重篤な有害事象、中止に至った有害事象及び注目すべき有害事象の発現割合に臨床的に意味のある差はみられなかった。12 歳以上のインヒビター保有の治験参加者を対象としたマルスタシマブ投与は、既知の安全性プロファイルと比較して新たな安全性上の懸念は認められなかった。

詳細は M2.5.5 を参照。

2. 用法及び用量（案）とその設定根拠

2.1. 用法及び用量（案）（取り消し線箇所を削除し、下線部を追記）

通常、12歳以上かつ体重~~35kg~~25kg以上の患者には、マルスタシマブ（遺伝子組換え）として初回に300mgを皮下投与し、以降は1週間隔で1回150mgを皮下投与する。なお、体重50kg以上で効果不十分な場合には、1週間隔で1回300mgに増量して皮下投与できる。

2.2. 用法及び用量（案）の設定根拠

2.2.1. 体重下限の変更

対象患者の体重下限については、安全性が確認されている体重換算の用量 6 mg/kg を考慮した体重の下限は 25 kg であること、臨床試験で体重 25 kg 以上 35 kg 未満の青年治験参加者 4 例（インヒビター保有患者 2 例、インヒビター非保有患者 2 例）にマルスタシマブ 150 mg を週 1 回投与した際の有効性は全体集団と同様で、安全性上の懸念は認められなかったことから、インヒビターの有無にかかわらず、対象患者の体重下限を 35 kg から 25 kg に変更した。

詳細は M2.7.3.4 を参照。

2.2.2. インヒビター保有患者に対する用法・用量の設定根拠

B7841005 試験において、12 歳以上の血友病 A 又は血友病 B の治験参加者の用法・用量はインヒビターの有無によらず同様としていた。1 項に示した通り、B7841005 試験の結果から、12 歳

以上のインヒビター保有の血友病 A 又は血友病 B の治験参加者に対するマルスタシマブの有効性及び安全性が確認されている。

インヒビター保有の血友病 A 及び血友病 B 患者の疫学的背景や出血傾向の病態、治療コンセプト等は、国内外で同様である（M2.5.1）。また、インヒビター保有患者に対するマルスタシマブの有効性及び安全性は部分集団（年齢、血友病型、人種、民族、地理的地域）間で一貫していた。B7841005 試験の結果において、インヒビター非保有患者における PK 及び PD は日本人と外国人で大きな違いは認められず（初回承認申請資料 M2.7.2）、インヒビター保有患者における PK 及び PD はインヒビター非保有患者と臨床的に意味のある差は認められなかった（M2.7.2）。以上から、外因性及び内因性民族的要因によるマルスタシマブの有効性及び安全性への影響は大きくないと考えられ、マルスタシマブに関する臨床試験の成績は青年及び成人の日本人のインヒビター保有血友病患者に一般化可能と考える。

詳細は M2.7.3.4 を参照。

使用上の注意（案）設定根拠

今回の製造販売承認事項一部変更承認申請に当たり、現行の添付文書を変更する箇所及びその設定根拠を以下に示す。現行の添付文書に追記する箇所を下線で示し、削除する箇所を取消し線で示した。なお、現行の添付文書の内容に変更がない項目は記載を省略した。

5. 効能又は効果に関連する注意

本剤は、血液凝固第Ⅷ因子又は第Ⅸ因子に対するインヒビターの有無によらず有効性が確認されている。［17.1.1-17.1.3参照］

［設定根拠］

国際共同第 3 相臨床試験（B7841005 試験及び B7841007 試験）の結果に基づき設定した。

8. 重要な基本的注意

8.1 本剤の臨床試験において、重篤な血栓塞栓性事象の発現が認められている。血栓塞栓性事象があらわれる可能性があるので、血栓塞栓性事象の既往又は危険因子の有無を慎重に確認した上で、本剤の投与を開始すること。また、患者に対し、血栓塞栓性事象の兆候や症状について十分説明するとともに、以下の注意事項の重要性についても理解を得た上で投与を開始すること。［1.1、1.2、9.1.1、9.1.2、11.1.1、15.2.1、15.2.2 参照］

8.2 バイパス止血製剤（活性型第Ⅶ因子製剤、活性型プロトロンビン複合体製剤、乾燥濃縮人血液凝固第Ⅹ因子加活性化第Ⅶ因子製剤）、血液凝固第Ⅷ因子又は第Ⅸ因子製剤による補充療法から本剤に切り替える場合は、切り替え前の製剤の半減期を考慮し、本剤投与開始前の適切な時期に中止すること。［15.2.2 参照］

8.3 バイパス止血製剤又は血液凝固因子製剤以外の血友病治療薬から本剤に切り替える場合の指針となる臨床試験データは得られていない。バイパス止血製剤又は血液凝固因子製剤以外の血友病治療薬から本剤に切り替える場合は、その製剤の半減期に基づき適切な休薬期間（少なくとも半減期の 5 倍の期間）の設定を考慮するなどし、本剤の投与を開始すること。休薬期間中は、必要に応じてバイパス止血製剤又は血液凝固因子製剤による補充療法を行うこと。

8.4 本剤による治療期間中に出血が発現した場合は、以下の点に注意すること。

8.4.1 必要に応じてバイパス止血製剤、血液凝固第Ⅷ因子又は第Ⅸ因子製剤の投与を行うこと。その場合は本剤との併用投与が可能であるが、各~~血液凝固因子~~製剤の電子添文や最新のガイドラインに従って投与し、投与量は、承認されている最低用量を目安として出血部位や程度に応じて判断すること。さらに、以下の点にも注意すること。［15.2.2 参照］

(1) 活性型第Ⅶ因子製剤については、承認されている用法・用量の範囲内で使用し、初回投与量は 90μg/kg、その後は約 2 時間ごとを超えない投与頻度で 1 回投与量として 60～90μg/kg を投与することが望ましい。

(2) 活性型プロトロンビン複合体製剤については、24 時間以内の最高用量は 100 単位/kg を上限とすることが望ましい。

8.4.2 バイパス止血製剤、血液凝固第Ⅷ因子又は第Ⅸ因子製剤の自己注射が必要になった場合に備え、バイパス止血製剤又は血液凝固因子製剤の投与間隔及び投与量について患者又は介護者に説明すること。

8.4.3 止血を目的とした本剤の追加投与及び用量変更は行わないこと。［7.1 参照］

8.4.4 血液凝固系検査等により患者の状態を注意深く観察し、異常が認められた場合は本剤の投与を中止し適切な処置を行うこと。

8.5 大手術時における本剤の有効性及び安全性は確立されていないため、大手術を行う場合は、本剤の投与を中止し、バイパス止血製剤又は血液凝固因子製剤を用いた標準治療を行い、周術期における静脈血栓症発現のリスクを管理すること。本剤の投与を再開する場合は、術後の血栓塞栓症リスク因子の有無や、その他の止血製剤及び併用薬の使用等、患者の全身状態を考慮すること。なお、抜歯等の小手術では本剤の用量変更又は投与中止の必要はない。

8.6 本剤による治療中の患者において、過敏症反応の可能性がある発疹及びそう痒症の皮膚症状が報告されている。重度の過敏症反応が認められた場合には、本剤の投与を中止し、速やかに適切な処置を行うこと。［11.1.2 参照］

8.7 自己注射にあたっては、投与法について十分な教育訓練を実施したのち、患者又は介護者が確実に投与できることを確認した上で、医師の管理指導の下で実施すること。また、患者又は介護者に対し、自己注射後に何らかの異常が認められた場合は、速やかに医療機関へ連絡するよう指導すること。適用後、自己注射の継続が困難な状況となる可能性がある場合には、医師の管理の下で慎重に観察するなど、適切な対応を行うこと。

［設定根拠］

8.1 変更なし

8.2～8.3 CCDS（4.2. Posology and method of administration）に基づき設定し、バイパス止血製剤の例として国内で使用されている 3 製剤を記載した。

8.4.1 CCDS（4.2. Posology and method of administration）及び国際共同第 3 相臨床試験（B7841005 試験及び B7841007 試験）の治験実施計画書に基づき、各バイパス止血製剤の注意事項を設定した。

8.4.2 CCDS（4.2. Posology and method of administration）に基づき設定した。

8.4.3～8.4.4 変更なし

8.5 CCDS（4.2. Posology and method of administration）に基づき設定した。

8.6～8.7 変更なし

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 血栓塞栓性事象の既往又は危険因子を有する患者

本剤投与により血栓塞栓性事象のリスクが高まる可能性がある。投与に際しては有益性と危険性を十分考慮すること。［1.1、1.2、8.1、11.1.1、15.2.1、15.2.2 参照］

9.1.2 組織因子が過剰に発現している状態にある患者

組織因子が過剰に発現している状態（進行したアテローム性疾患、癌、挫滅、敗血症、炎症病態等）では、本剤投与により血栓塞栓性事象又は播種性血管内凝固症候群（DIC）のリスクが高まる可能性がある。［1.1、1.2、8.1、11.1.1、15.2.1、15.2.2 参照］

9.4 生殖能を有する者

妊娠する可能性のある女性には、本剤投与中及び最終投与後 1 ヵ月間において避妊する必要性及び適切な避妊法について説明すること。

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。ラットの胚・胎児発生に関する試験において、最大臨床用量（本剤 300mg を週 1 回皮下投与）における AUC の 4.3 倍に相当する用量で影響は認められなかったが、17 倍に相当する用量で胚・胎児毒性（骨格奇形及び骨格変異並びに着床後胚損失の増加）が認められた。一方、ウサギの胚・胎児発生に関する試験では、最大臨床用量（本剤 300mg を週 1 回皮下投与）における AUC の 32 倍に相当する用量で影響は認められなかった。~~雌動物を用いた生殖発生毒性試験は実施していない。~~また、一般にヒト IgG は胎盤を通過することが知られており、~~いる。~~本剤を妊婦に投与した場合、胎児及び出生児における血栓形成リスクが否定できない。［15.2.1、15.2.2 参照］

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤のヒト乳汁中への移行性は不明であるが、一般にヒト IgG はヒト乳汁中に移行することが知られている。

9.7 小児等

12 歳未満の小児を対象とした臨床試験は実施していない。

9.8 高齢者

患者の状態を観察しながら慎重に投与すること。一般に、生理機能が低下していることが多い。

［設定根拠］

9.1.1 CCDS（4.4. Special warnings and precautions for use）に基づき、リスクを明記した。

9.1.2、9.4 変更なし

9.5 CCDS（4.6. Fertility, pregnancy and lactation 及び 5.3. Preclinical safety data）に基づき更新した。

9.6～9.8 変更なし

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 血栓塞栓性事象（~~頻度不明~~ 0.6%）

［1.1、1.2、8.1、9.1.1、9.1.2、15.2.1、15.2.2 参照］

11.1.2 **ショック、アナフィラキシー**（いずれも頻度不明）

発疹、そう痒、呼吸困難、喘鳴、血圧低下等の症状が認められた場合には投与を中止し、適切な処置を行うこと。［8.6 参照］

11.2 **その他の副作用**

	3%以上	3%未満	~~頻度不明~~
感染症および寄生虫症		丹毒	
血液およびリンパ系障害		好中球減少症	
神経系障害		頭痛、浮動性めまい	
胃腸障害~~消化器~~		痔核、腹痛	
皮膚および皮下組織障害	~~そう痒症~~	発疹、そう痒症	~~発疹[a)]~~
筋~~・~~骨格系および結合組織障害		関節痛、出血性関節症	
先天性、家族性および遺伝性障害		リンパ管奇形	
一般・全身障害~~及~~および投与部位の状態	注射部位反応（紅斑、そう痒感、腫脹、出血、浮腫、硬結、疼痛等）（11.4~~11.2~~%）	~~挫傷、~~疲労、末梢腫脹	
臨床検査	フィブリンDダイマー増加、プロトロンビンフラグメント1・2増加	~~プロトロンビンフラグメント1・2増加、フィブリンDダイマー増加~~アラニンアミノトランスフェラーゼ増加	
傷害、中毒および処置合併症		挫傷	

~~a) インヒビター保有患者において認められた~~

［設定根拠］

11.1.1 国際共同第 3 相臨床試験（B7841005 試験及び B7841007 試験）において、本剤との因果関係が否定できないと治験責任医師が評価した事象の発現頻度を追記した。

11.1.2 変更なし

11.2 国際共同第 3 相臨床試験（B7841005 試験及び B7841007 試験）において、本剤との因果関係が否定できないと治験責任医師が評価した事象について、この評価に基づく発現頻度と共に記載した。

15. **その他の注意**

15.1 **臨床使用に基づく情報**

15.1.1 ~~インヒビター非保有の~~血友病 A 又は血友病 B 患者を対象とした国際共同第Ⅲ相臨床試験（B7841005 試験）及び B7841005 試験を完了した患者を対象とした国際共同第Ⅲ相臨床試験（B7841007 試験）の併合解析において、抗薬物抗体（ADA）の評価が可能な ~~116~~167 例中 ~~23~~39 例（~~19.8~~23.4%）で ADA の発現が認められ、インヒビター非保有患者では 23.3%（27/116 例）、インヒビター保有患者では 23.5%（12/51 例）であった。ADA 発現例のうち 66.7%（26/39 例）は一過性、30.8%（12/39 例）は持続性であり、97.4%（38/39 例）はデータカットオフ時までに消失した。ADA 発現例における中和抗体（NAb）の発現割合は 20.5%（8/39 例）であり、インヒビター非保有患者では 22.2%（6/27 例）、インヒビター保有患者では 16.7%（2/12 例）であった。~~このうち 6 例（5.2%）は中和抗体（NAb）陽性であった。~~認められた NAb の大部分（87.5%）は一過性で、NAb はデータカットオフ時までに

消失した。B7841005 試験の 12 ヵ月間の本剤投与期間において、ADA の発現が認められた患者では ADA の発現が認められなかった患者と比較して、本剤の平均血漿中濃度に低下傾向（約 10%～36%）が認められたが、ADA 及び NAb の発現による本剤の有効性及び安全性に対する影響を示唆する成績は得られていない ~~ADA 及び NAb の発現は大部分が一過性で、試験終了時に ADA 陽性であった 1 例を除き、ADA 及び NAb の発現は試験終了時までに消失した[1)]。B7841005 試験を完了した患者を対象とした国際共同第Ⅲ相臨床試験（B7841007 試験）では、ADA の評価が可能な 44 例中 1 例（2.3%）で ADA の発現が認められたが、NAb 陰性であった[1)]~~。［17.1.1~~、~~17.1.3~~2~~参照］

15.1.2 免疫寛容導入療法と本剤を併用した際の安全性及び有効性は確立していない。

15.2 非臨床試験に基づく情報

15.2.1 ラットを用いたマルスタシマブの 6 ヵ月間反復投与毒性試験において、~~AUC 比較で臨床曝露量~~最大臨床用量（本剤 300mg を週 1 回皮下投与~~時~~）における AUC の 7.6 倍に相当する用量から血栓形成が認められ、血栓形成に対する無影響量及び安全域は得られていない。［1.1、8.1、9.1.1、9.1.2、9.5、11.1.1 参照］

15.2.2 ラットを用いた試験において、最大臨床用量（本剤 300mg を週 1 回皮下投与）における C_{max} の 27 倍に相当する用量のマルスタシマブと最大臨床用量（270μg/kg）を投与した時の定常状態での C_{max} を上回るよう設定した用量（3mg/kg）の活性型血液凝固第Ⅶ因子製剤を併用投与した結果、単独投与と比較して肺及び投与部位での血栓・塞栓の発現頻度の増加及び重症度の悪化が認められた。一方、27 倍（C_{max} 比較）に相当する用量のマルスタシマブと 0.8mg/kg の活性型血液凝固第Ⅶ因子製剤の併用投与、3 倍（C_{max} 比較）に相当する用量のマルスタシマブと臨床用量（100U/kg/日）と同用量の活性型プロトロンビン複合体製剤の併用投与、及び 2 倍（C_{max} 比較）に相当するマルスタシマブと出血時の最大臨床用量（活性化人血液凝固第Ⅶ因子として 180μg/kg/日）と同用量の乾燥濃縮人血液凝固第Ⅹ因子加活性化第Ⅶ因子製剤の併用投与では、単独投与と比較して明確な影響は認められなかった[2)]。［1.1、8.1、8.2、8.4.1、9.1.1、9.1.2、9.5、11.1.1 参照］

［設定根拠］

15.1.1 国際共同第 3 相臨床試験（B7841005 試験及び B7841007 試験）の結果及び CCDS（5.1. Pharmacodynamic properties）に基づき更新した。

15.1.2 CCDS（4.2. Posology and method of administration）に基づき設定した。

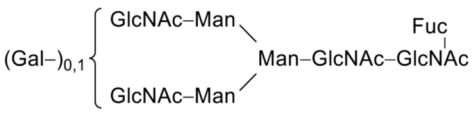
15.2.1 記載整備

15.2.2 CCDS（5.3. Preclinical safety data）に基づき設定した。

初回承認申請資料において提出済みである。

（現行）

化学名・別名	一般名：マルスタシマブ（遺伝子組換え） Marstacimab (Genetical Recombination) 本質：マルスタシマブは，遺伝子組換え抗組織因子経路インヒビター（TFPI）モノクローナル抗体であり，ヒト IgG1 に由来する。H 鎖の 3 つのアミノ酸残基が置換（L237A，L238A，G240A）され，C 末端の K450 は除去されている。マルスタシマブは，CHO 細胞により産生される。マルスタシマブは，449 個のアミノ酸残基からなる H 鎖（γ1 鎖）2 本及び 218 個のアミノ酸残基からなる L 鎖（λ鎖）2 本で構成される糖タンパク質（分子量：約 146,000）である。
構造式	アミノ酸配列及びジスルフィド結合 H鎖 EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVSA ISGSGGSTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAILG ATSLSAFDIW GQGTMVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPEAAGA PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPG L鎖 QSVLTQPPSV SGAPGQRVTI SCTGSSSNIG AGYDVHWYQQ LPGTAPKLLI YGNSNRPSGV PDRFSGSKSG TSASLAITGL QAEDEADYYC QSYDSSLSGS GVFGGGTKLT VLGQPKAAPS VTLFPPSSEE LQANKATLVC LISDFYPGAV TVAWKADSSP VKAGVETTTP SKQSNNKYAA SSYLSLTPEQ WKSHRSYSCQ VTHEGSTVEK TVAPTECS H鎖N300：糖鎖結合 L鎖Q1：部分的ピログルタミン酸 H鎖C223－L鎖C217，H鎖C229－H鎖C229，H鎖C232－H鎖C232：ジスルフィド結合

<table>
<tr><td></td><td>主な糖鎖の推定構造

</td></tr>
<tr><td>効能・効果</td><td>血液凝固第 VIII 因子又は第 IX 因子に対するインヒビターを保有しない先天性血友病患者における出血傾向の抑制</td></tr>
<tr><td>用法・用量</td><td>通常、12 歳以上かつ体重 35kg 以上の患者には、マルスタシマブ（遺伝子組換え）として初回に 300mg を皮下投与し、以降は 1 週間隔で 1 回 150mg を皮下投与する。なお、体重 50kg 以上で効果不十分の場合には、1 週間隔で 1 回 300mg に増量して皮下投与できる。</td></tr>
<tr><td>劇薬等の指定</td><td></td></tr>
<tr><td>市販名及び
有効成分・分量</td><td>原体：マルスタシマブ（遺伝子組換え）
製剤：
販売名　：ヒムペブジ皮下注 150mg ペン
有効成分：1 製剤 1mL 中マルスタシマブ（遺伝子組換え）150mg</td></tr>
<tr><td>毒性</td><td>単回投与毒性
<table>
<tr><th>概略の致死量</th><th>静脈内投与</th><th>皮下投与</th></tr>
<tr><td>ラット（雌雄）</td><td>>1000 mg/kg</td><td>>300 mg/kg</td></tr>
<tr><td>サル（雌雄）</td><td>>500 mg/kg</td><td>>90 mg/kg</td></tr>
</table>
反復投与毒性
<table>
<tr><th>動物種</th><th>投与期間</th><th>投与経路</th><th>投与量 (mg/kg/週)</th><th>無毒性量 (mg/kg/週)</th><th>主な所見</th></tr>
<tr><td rowspan="5">ラット</td><td rowspan="2">8日</td><td>静脈内</td><td>0, 3, 30, 90</td><td>90（最大耐量）</td><td>30 mg/kg/週以上：D-ダイマー増加，グロブリン増加，A/G比低下</td></tr>
<tr><td>皮下</td><td>3</td><td>3（最大耐量）</td><td>3 mg/kg/週：D-ダイマー増加，皮下投与部位の色調異常（剖検所見）ならびに混合性細胞浸潤，壊死および出血（病理組織学的所見）</td></tr>
<tr><td rowspan="2">3ヵ月</td><td>静脈内</td><td>0, 60, 180, 1000</td><td>1000</td><td>60 mg/kg/週以上：フィブリノゲン減少，aPTT延長
1000 mg/kg/週：PT短縮，アルブミン減少，グロブリン増加，総タンパク増加，A/G比低下</td></tr>
<tr><td>皮下</td><td>0, 180</td><td>180</td><td>180 mg/kg/週：フィブリノゲン減少，PT短縮，aPTT延長</td></tr>
<tr><td>6ヵ月</td><td>静脈内</td><td>0, 60, 180, 1000</td><td>1000</td><td>60 mg/kg/週以上，フィブリノゲン減少，aPTT延長，D-ダイマー増加，グロブリン増加，肺の血栓/塞栓，細胞浸潤および好塩基性/非好塩基性異物，尾静脈の血栓/塞栓
180 mg/kg/週以上：総タンパク増加，A/G比低下
1000 mg/kg/週：PT延長，アルブミン減少</td></tr>
</table></td></tr>
</table>

	サル	8日	静脈内	0, 3, 30, 90	90（最大耐量）	3 mg/kg/週以上：D-ダイマー増加
			皮下	0, 3	3（最大耐量）	3 mg/kg/週：D-ダイマー増加
		3ヵ月	静脈内	0, 30, 90, 500	500	30 mg/kg/週以上：フィブリノゲン減少，PT延長，D-ダイマー増加，総タンパク増加，グロブリン増加，A/G比低下 500 mg/kg/週：aPTT延長
			皮下	0, 90	90	90 mg/kg/週：フィブリノゲン減少，PT延長，D-ダイマー増加，総タンパク増加，グロブリン増加，A/G比低下
副作用	**主な副作用の発現率** 副作用の種類　例数　% 注射部位そう痒感　4/116　3.4 そう痒症　4/116　3.4 注射部位紅斑　3/116　2.6 注射部位腫脹　3/116　2.6 プロトロンビンフラグメント１・２増加　3/116　2.6					
会社	ファイザー株式会社					

（追加）

化学名・別名	
構造式	
効能・効果	先天性血友病患者における出血傾向の抑制
用法・用量	通常、12 歳以上かつ体重 25kg 以上の患者には、マルスタシマブ（遺伝子組換え）として初回に 300mg を皮下投与し、以降は 1 週間隔で 1 回 150mg を皮下投与する。なお、体重 50kg 以上で効果不十分な場合には、1 週間隔で 1 回 300mg に増量して皮下投与できる。 （下線部を変更）
劇薬等の指定	
市販名及び有効成分・分量	
毒性	
副作用	**主な副作用の発現率** 副作用の種類 / 例数 / % 注射部位反応（紅斑、そう痒感、腫脹、出血、浮腫，硬結、疼痛等） 19/167 11.4 フィブリン D ダイマー増加 7/167 4.2 プロトロンビンフラグメント 1・2 増加 6/167 3.6 そう痒症 4/167 2.4 発疹 4/167 2.4 アラニンアミノトランスフェラーゼ増加 2/167 1.2 （下線部を変更）
会社	ファイザー株式会社

添付資料番号	報告書番号	タイトル	著者	試験実施期間	試験実施場所	報告書の種類(国内/外国)	掲載誌	評価/参考の別	電子データの提出
第3部　品質に関する文書									
		該当資料なし							
第4部　非臨床試験報告書									
4.2.1　薬理試験									
4.2.1.1　効力を裏付ける試験									
4.2.1.1.1	PF-06741086_[redacted]_042724	IN VITRO CHARACTERIZATION OF PF-06741086 ACTIVITY IN HUMAN HEMOPHILIA PLASMA WITH HEMLIBRA-EMICIZUMAB IN A TGA ASSAY	[redacted]	20[redacted]年[redacted]月～[redacted]月	Pfizer (Cambridge)，米国	外国	社内資料	評価	無
4.2.1.2　副次的薬理試験									
		該当資料なし							
4.2.1.3　安全性薬理試験									
		該当資料なし							
4.2.1.4　薬力学的薬物相互作用試験									
		該当資料なし							
4.2.2　薬物動態試験									
4.2.2.1　分析法及びバリデーション報告書									
4.2.2.1.1	15-[redacted]20 (PF-06741086_[redacted]_031711)	The Validation of an ELISA for the Determination of PF-06741086 in New Zealand White Rabbit K_2EDTA Plasma	[redacted]	20[redacted]年[redacted]月～20[redacted]年[redacted]月	[redacted]米国	外国	社内資料	評価	無
4.2.2.2　吸収									
		該当資料なし							
4.2.2.3　分布									
		該当資料なし							
4.2.2.4　代謝									
		該当資料なし							
4.2.2.5　排泄									
		該当資料なし							
4.2.2.6　薬物動態学的薬物相互作用（非臨床）									
		該当資料なし							
4.2.2.7　その他の薬物動態試験									
		該当資料なし							
4.2.3　毒性試験									
4.2.3.1　単回投与毒性試験									
		該当資料なし							
4.2.3.2　反復投与毒性試験									
		該当資料なし							
4.2.3.3　遺伝毒性試験									
4.2.3.3.1　*In Vitro* 試験									
		該当資料なし							
4.2.3.3.2　*In Vivo* 試験									
		該当資料なし							
4.2.3.4　がん原性試験									
4.2.3.4.1　長期がん原性試験									
		該当資料なし							
4.2.3.4.2　短期又は中期がん原性試験									
		該当資料なし							
4.2.3.4.3　その他の試験									
		該当資料なし							
4.2.3.5　生殖発生毒性試験									
4.2.3.5.1　受胎能及び着床までの初期胚発生に関する試験									
4.2.3.5.1.1	[redacted]PZ257	INTRAVENOUS INJECTION FEMALE FERTILITY STUDY OF PF-06741086 IN WISTAR HAN RATS	[redacted]	20[redacted]年[redacted]月～20[redacted]年[redacted]月	Pfizer (Groton), 米国	外国	社内資料	評価	無
4.2.3.5.2　胚・胎児発生に関する試験									
4.2.3.5.2.1	[redacted]PZ187	INTRAVENOUS INJECTION EMBRYO-FETAL DEVELOPMENT STUDY OF PF-06741086 IN PREGNANT WISTAR HAN RATS	[redacted]	20[redacted]年[redacted]月～20[redacted]年[redacted]月，20[redacted]年[redacted]月	Pfizer (Groton), 米国	外国	社内資料	評価	無
4.2.3.5.2.2	[redacted]PZ188	INTRAVENOUS INJECTION DOSE RANGE-FINDING STUDY OF PF-06741086 IN PREGNANT NEW ZEALAND WHITE RABBITS	[redacted]	20[redacted]年[redacted]月	Pfizer (Groton), 米国	外国	社内資料	参考	無
4.2.3.5.2.3	[redacted]PZ233	INTRAVENOUS INJECTION EMBRYO-FETAL DEVELOPMENT STUDY OF PF-06741086 IN PREGNANT NEW ZEALAND WHITE RABBITS	[redacted]	20[redacted]年[redacted]月～20[redacted]年[redacted]月	Pfizer (Groton), 米国	外国	社内資料	評価	無
4.2.3.5.3　出生前及び出生後の発生並びに母体の機能に関する試験									

添付資料番号	報告書番号	タイトル	著者	試験実施期間	試験実施場所	報告書の種類(国内/外国)	掲載誌	評価/参考の別	電子データの提出
		該当資料なし							
4.2.3.5.4 新生児を用いた試験									
		該当資料なし							
4.2.3.6 局所刺激性試験									
		該当資料なし							
4.2.3.7 その他の毒性試験									
4.2.3.7.1 抗原性試験									
		該当資料なし							
4.2.3.7.2 免疫毒性試験									
		該当資料なし							
4.2.3.7.3 毒性発現の機序に関する試験									
		該当資料なし							
4.2.3.7.4 依存性試験									
		該当資料なし							
4.2.3.7.5 代謝物の毒性試験									
		該当資料なし							
4.2.3.7.6 不純物の毒性試験									
		該当資料なし							
4.2.3.7.7 その他の試験									
		該当資料なし							
4.3 参考文献									
		該当資料なし							
第5部 臨床試験報告書									
5.2 全臨床試験一覧表									
		全臨床試験一覧表	—	—	—	—	—	—	—
5.3 試験報告書及び関連情報									
5.3.1 生物薬剤学試験報告書									
5.3.1.1 バイオアベイラビリティ（BA）試験報告書									
		該当資料なし							
5.3.1.2 比較BA試験及び生物学的同等性（BE）試験報告書									
		該当資料なし							
5.3.1.3 *In Vitro - In Vivo* の関連を検討した試験報告書									
		該当資料なし							
5.3.1.4 生物学的及び理化学的分析法検討報告書									
5.3.1.4.1	B7847009	THE VALIDATION OF AN ECL METHOD FOR THE DETERMINATION OF ANTI-PF-06741086 ANTIBODIES IN HUMAN SODIUM CITRATE PLASMA, Amendment 1	United-Power Pharm Tech Co., Ltd.	2025年9月3日	中国	外国	—	参考	無
5.3.1.4.2	B7847010	THE VALIDATION OF AN ECL METHOD FOR THE DETERMINATION OF NEUTRALIZING ANTI-PF-06741086 ANTIBODIES IN SODIUM CITRATE HUMAN PLASMA, Amendment 1	United-Power Pharm Tech Co., Ltd.	2025年8月29日	中国	外国	—	参考	無
5.3.1.4.3	B7849001	The Validation of an ECL Assay Method for the Determination of PF-06741086 in Sodium Citrate Human Plasma, Amendment 3	QPS, LLC	2024年8月6日	米国	外国	—	参考	無
		The Validation of an ECL Assay Method for the Determination of PF-06741086 in Sodium Citrate Human Plasma, Amendment 4	QPS, LLC	2025年9月4日	米国	外国	—	参考	無
5.3.1.4.4	B7849002	THE VALIDATION OF AN ELECTROCHEMILUMINESCENCE (ECL) METHOD FOR THE DETERMINATION OF PF-06741086 IN HUMAN SODIUM CITRATE HUMAN PLASMA, Amendment 2	United-Power Pharm Tech Co., Ltd.	2025年5月28日	中国	外国	—	参考	無
		THE VALIDATION OF AN ELECTROCHEMILUMINESCENCE (ECL) METHOD FOR THE DETERMINATION OF PF-06741086 IN HUMAN SODIUM CITRATE HUMAN PLASMA, Amendment 3	United-Power Pharm Tech Co., Ltd.	2025年9月4日	中国	外国	—	参考	無
5.3.1.4.5	B7841005	BIOANALYTICAL STUDY REPORT: THE DETERMINATION OF ANTI-PF-06741086 ANTIBODIES IN SODIUM CITRATE HUMAN PLASMA SAMPLES BY AN ECL METHOD FROM PFIZER CLINICAL PROTOCOL B7841005, Amendment 1	United-Power Pharm Tech Co., Ltd.	2025年8月29日	中国	外国	—	参考	無
		BIOANALYTICAL STUDY REPORT: THE DETERMINATION OF PF-06741086 IN SODIUM CITRATE HUMAN PLASMA SAMPLES BY ECL FROM PFIZER CLINICAL PROTOCOL B7841005, AMENDMENT 1	United-Power Pharm Tech Co., Ltd.	2025年9月4日	中国	外国	—	参考	無
		FINAL BIOANALYTICAL STUDY REPORT: THE DETERMINATION OF PF-06741086 IN SODIUM CITRATE HUMAN PLASMA SAMPLES BY ECL FROM PFIZER CLINICAL PROTOCOL B7841005	QPS, LLC	2025年9月4日	米国	外国	—	参考	無
		FINAL BIOANALYTICAL STUDY REPORT: THE DETERMINATION OF ANTI-PF-06741086 ANTIBODIES IN HUMAN SODIUM CITRATE PLASMA SAMPLES BY ECL FROM PFIZER CLINICAL PROTOCOL	QPS, LLC	2025年9月4日	米国	外国	—	参考	無

添付資料番号	報告書番号	タイトル	著者	試験実施期間	試験実施場所	報告書の種類(国内/外国)	掲載誌	評価/参考の別	電子データの提出
		FINAL BIOANALYTICAL STUDY REPORT: THE DETERMINATION OF NEUTRALIZING ANTI-PF-06741086 ANTIBODIES IN HUMAN SODIUM CITRATE PLASMA SAMPLES BY ECL FROM PFIZER CLINICAL PROTOCOL B7841005	QPS, LLC	2025年9月4日	米国	外国	－	参考	無
		BIOMARKER BIOANALYTICAL STUDY REPORT: THE DETERMINATION OF TOTAL TFPI IN HUMAN SODIUM CITRATE PLASMA SAMPLES BY IMMUNOAFFINITY LC/MS FROM PFIZER	Thermo Fisher Scientific PPD Laboratory Services Bioanalytical Lab	2025年5月30日	米国	外国	－	参考	無
5.3.1.4.6	B7841007	INTERIM BIOANALYTICAL STUDY REPORT: THE DETERMINATION OF PF-06741086 IN SODIUM CITRATE HUMAN PLASMA SAMPLES BY ECL FROM PFIZER CLINICAL PROTOCOL B7841007	QPS, LLC	2025年9月5日	米国	外国	－	参考	無
		INTERIM BIOANALYTICAL STUDY REPORT: THE DETERMINATION OF ANTI-PF-06741086 ANTIBODIES IN HUMAN SODIUM CITRATE PLASMA SAMPLES BY ECL FROM PFIZER CLINICAL PROTOCOL	QPS, LLC	2025年9月5日	米国	外国	－	参考	無
		INTERIM BIOANALYTICAL STUDY REPORT: THE DETERMINATION OF NEUTRALIZING ANTI-PF-06741086 ANTIBODIES IN HUMAN SODIUM CITRATE HUMAN PLASMA SAMPLES BY ECL FROM PFIZER CLINICAL PROTOCOL B7841007	QPS, LLC	2025年9月4日	米国	外国	－	参考	無
		BIOANAL YTICAL STUDY INTERIM REPORT: THE DETERMINATION OF ANTI-PF-06741086 ANTIBODIES IN SODIUM CITRATE HUMAN PLASMA SAMPLES BY AN ECL METHOD FROM PFIZER CLINICAL PROTOCOL B7841007	United-Power Pharm Tech Co., Ltd.	2025年9月4日	中国	外国	－	参考	無
		BIOANALYTICAL STUDY INTERIM REPORT: THE DETERI\DNATION OF NEUTRALIZING ANTI-PF-06741086 ANTIBODIBS IN SODIUM CITRATE HUMAN PLASMA SAMPLES BY AN ECL METHOD FROM PFIZER CLINICAL PROTOCOL B7841007	United-Power Pharm Tech Co., Ltd.	2025年9月4日	中国	外国	－	参考	無
		BIOMARKER BIOANALYTICAL STUDY REPORT: THE DETERMINATION OF TOTAL TFPI IN HUMAN SODIUM CITRATE PLASMA SAMPLES BY IMMUNOAFFINITY LC/MS FROM PFIZER CLINICAL PROTOCOL B7841007, INTERIM No. 1	Thermo Fisher Scientific PPD Laboratory Services Bioanalytical Lab	2025年8月27日	米国	外国	－	参考	無
5.3.1.4.7	B7841008	INTERIM BIOANALYTICAL STUDY REPORT: THE DETERMINATION OF PF-06741086 IN SODIUM CITRATE HUMAN PLASMA SAMPLES BY ECL FROM PFIZER CLINICAL PROTOCOL B7841008	QPS, LLC	2025年9月8日	米国	外国	－	参考	無
		INTERIM BIOANALYTICAL STUDY REPORT: THE DETERMINATION OF ANTI-PF-06741086 ANTIBODIES IN SODIUM CITRATE HUMAN PLASMA SAMPLES BY ECL FROM PFIZER CLINICAL PROTOCOL	QPS, LLC	2025年9月8日	米国	外国	－	参考	無
		INTERIM BIOANALYTICAL STUDY REPORT: THE DETERMINATION OF NEUTRALIZING ANTI-PF-06741086 ANTIBODIES IN HUMAN SODIUM CITRATE HUMAN PLASMA SAMPLES BY ECL FROM PFIZER CLINICAL PROTOCOL B7841008	QPS, LLC	2025年9月5日	米国	外国	－	参考	無
		BIOANALYTICAL STUDY INTERIM REPORT: THE DETERMINATION OF PF-06741086 IN SODIUM CITRATE HUMAN PLASMA SAMPLES BY ECL FROM PFIZER CLINICAL PROTOCOL B7841008	United-Power Pharm Tech Co., Ltd.	2025年9月4日	中国	外国	－	参考	無
		BIOANAL YTICAL STUDY INTERIM REPORT: THE DETERMINATION OF ANTI-PF-06741086 ANTIBODIES IN SODIUM CITRATE HUMAN PLASMA SAMPLES BY AN ECL METHOD FROM PFIZER CLINICAL PROTOCOL B7841008	United-Power Pharm Tech Co., Ltd.	2025年8月29日	中国	外国	－	参考	無
		BIOMARKER BIOANALYTICAL STUDY REPORT: THE DETERMINATION OF TOTAL TFPI IN HUMAN SODIUM CITRATE PLASMA SAMPLES BY IMMUNOAFFINITY LC/MS FROM PFIZER CLINICAL PROTOCOL B7841008, INTERIM No. 1	Thermo Fisher Scientific PPD Laboratory Services Bioanalytical Lab	2025年8月28日	米国	外国	－	参考	無
5.3.2 ヒト生体試料を用いた薬物動態関連の試験報告書									
5.3.2.1 血漿蛋白結合試験報告書									
		該当資料なし							
5.3.2.2 肝代謝及び薬物相互作用試験報告書									
		該当資料なし							
5.3.2.3 他のヒト生体試料を用いた試験報告書									
		該当資料なし							
5.3.3 臨床薬物動態（PK）試験報告書									
5.3.3.1 健康被験者におけるPK及び初期忍容性試験報告書									
		該当資料なし							
5.3.3.2 患者におけるPK及び初期忍容性試験報告書									
		該当資料なし							
5.3.3.3 内因性要因を検討したPK試験報告書									
		該当資料なし							
5.3.3.4 外因性要因を検討したPK試験報告書									

添付資料番号	報告書番号	タイトル	著者	試験実施期間	試験実施場所	報告書の種類(国内/外国)	掲載誌	評価/参考の別	電子データの提出
		該当資料なし							
5.3.3.5 ポピュレーションPK試験報告書									
5.3.3.5.1	PMAR-EQDD-B784a-DP3-1331-Supplement2-Japan-Amendment	Population pharmacokinetic and pharmacodynamic modeling of PF-06741086 (Marstacimab)	–	2026年5月26日	–	–	–	参考	有
5.3.4 臨床薬力学（PD）試験報告書									
5.3.4.1 健康被験者におけるPD試験及びPK/PD試験報告書									
		該当資料なし							
5.3.4.2 患者におけるPD試験及びPK/PD試験報告書									
		該当資料なし							
5.3.5 有効性及び安全性試験報告書									
5.3.5.1 申請する適応症に関する比較対照試験報告書									
		該当資料なし							
5.3.5.2 非対照試験報告書									
5.3.5.2.1	B7841005	An Open-Label Study in Adolescent and Adult Severe (Coagulation Factor Activity <1%) Hemophilia A Participants With or Without Inhibitors or Moderately Severe to Severe Hemophilia B Participants (Coagulation Factor Activity ≤2%) With or Without Inhibitors Comparing Standard Treatment to PF-06741086 Prophylaxis	–	2020年3月9日～2025年4月29日	ブルガリア、カナダ、中国、クロアチア、フランス、香港、インド、イタリア、日本、韓国、メキシコ、オマーン、ロシア、サウジアラビア、セルビア、南アフリカ、スペイン、台湾、トルコ、米国	国内及び外国	–	評価	有
5.3.5.2.2	B7841007	An Open-Label Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of Marstacimab Prophylaxis in Severe (Coagulation Factor Activity <1%) Hemophilia A Participants With or Without Inhibitors or Moderately Severe to Severe Hemophilia B Participants (Coagulation Factor Activity ≤2%) With or Without Inhibitors	–	2021年11月17日～2025年5月[redacted]日（データカットオフ日）	アルゼンチン、オーストラリア、カナダ、中国、クロアチア、フランス、香港、インド、イスラエル、イタリア、日本、韓国、メキシコ、オマーン、ロシア、セルビア、スロバキア、南アフリカ、スペイン、台湾、トルコ、英国、米国	国内及び外国	–	評価	有
5.3.5.2.3	B7841008	An Open-Label Study in Pediatric (<18 Years of Age), Severe Hemophilia A Participants (Coagulation Factor Activity <1%) With or Without Inhibitors or Moderately Severe to Severe Hemophilia B Participants (Coagulation Factor Activity ≤2%) With or Without Inhibitors Comparing 12 Months of Historical Standard Treatment to Marstacimab Prophylaxis	–	2022年12月[redacted]日～2025年5月[redacted]日（データカットオフ日）	アルゼンチン、オーストラリア、オーストリア、ブラジル、カナダ、中国、チェコ、デンマーク、ドイツ、インド、イスラエル、イタリア、日本、韓国、サウジアラビア、スロバキア、南アフリカ、スペイン、台湾、トルコ、英国	国内及び外国	–	参考	無
5.3.5.3 複数の試験成績を併せて解析した報告書					,				
5.3.5.3.1		Integrated Summary of Efficacy Tables	–	–	–	–	–	–	有
5.3.5.3.2		Integrated Summary of Safety Tables	–	–	–	–	–	–	有
5.3.5.3.3		Integrated Summary of Immunogenicity	–	–	–	–	–	–	有
5.3.5.4 その他の臨床試験報告書									
		該当資料なし							
5.3.6 市販後の使用経験に関する報告書									
	–	新医療用医薬品に関する安全性定期報告書(第2回)	–	–	–	国内	–		–
5.3.7 患者データ一覧表及び症例記録									
5.3.7.1	B7841005, B7841007	有害事象一覧表	–	–	–	外国	社内資料	-	-
5.3.7.2	B7841005, B7841007	重篤な有害事象一覧表	–	–	–	外国	社内資料	-	-
5.3.7.3	B7841005, B7841007	臨床検査値異常変動症例一覧表	–	–	–	外国	社内資料	-	-
5.4 参考文献									
5.4.1	–	Hemophilia: in review.	Zimmerman B, Valentino LA.	–	–	外国	Pediatr Rev	参考	無
5.4.2	–	Biology of tissue factor pathway inhibitor.	Wood JP, Ellery PER, Maroney SA, et al.	–	–	外国	Blood	参考	無
5.4.3	–	Factor VIII products and inhibitor development in severe hemophilia A.	Gouw SC, van der Bom JG, Ljung R, et al.	–	–	外国	N Engl J Med	参考	無
5.4.4	–	The safety and efficacy of recombinant human blood coagulation factor IX in previously untreated patients with severe or moderately severe hemophilia B.	Shapiro AD, Di Paola J, Cohen A, et al.	–	–	外国	Blood	参考	無
5.4.5	–	血液凝固異常症全国調査 令和6年度報告書.	エイズ予防財団	–	–	国内	–	参考	無

添付資料番号	報告書番号	タイトル	著者	試験実施期間	試験実施場所	報告書の種類(国内/外国)	掲載誌	評価/参考の別	電子データの提出
5.4.6	–	WFH Guidelines for the Management of Hemophilia, 3rd edition.	Srivastava A, Santagostino E, Dougall A, et al.	–	–	外国	Haemophilia	参考	無
5.4.7	–	Factor VIII gene (F8) mutation and risk of inhibitor development in nonsevere hemophilia A.	Eckhardt CL, van Velzen AS, Peters M; INSIGHT Study Group.	–	–	外国	Blood	参考	無
5.4.8	–	Inhibitor development and mortality in non-severe hemophilia A.	Eckhardt CL, Loomans JI, van Velzen AS; INSIGHT Study Group.	–	–	外国	J Thromb Haemost	参考	無
5.4.9	–	The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation.	Hay CRM, Brown S, Collins PW, et al.	–	–	外国	Br J Haematol	参考	無
5.4.10	–	The diagnosis and management of factor VIII and IX inhibitors: a guideline from the UK Haemophilia Centre Doctors' Organization (UKHCDO).	Hay CRM, Baglin TP, Collins PW, et al.	–	–	外国	Br J Haematol	参考	無
5.4.11	–	ノボセブンHI静注用1 mgシリンジ／ノボセブンHI静注用2 mgシリンジ／ノボセブンHI静注用5 mgシリンジ添付文書 2024年9月改訂（第2版）	ノボノルディスクファーマ株式会社	–	–	国内	–	参考	無
5.4.12	–	ファイバ静注用1000 添付文書 2024年7月改訂（第2版）	武田薬品工業株式会社	–	–	国内	–	参考	無
5.4.13	–	バイクロット配合静注用 添付文書 2022年8月改訂（第4版）	KMバイオロジクス株式会社	–	–	国内	–	参考	無
5.4.14	–	How I use bypassing therapy for prophylaxis in patients with hemophilia A and inhibitors.	Leissinger CA, Singleton T, Kruse-Jarres R.	–	–	外国	Blood	参考	無
5.4.15	–	ヘムライブラ皮下注 12 mg／ヘムライブラ皮下注 30 mg／ヘムライブラ皮下注 60 mg／ヘムライブラ皮下注 90 mg／ヘムライブラ皮下注 105 mg／ヘムライブラ皮下注 150 mg添付文書 2024年11月改訂（第4版）	中外製薬株式会社	–	–	国内	–	参考	無
5.4.16	–	Emicizumab treatment: impact on coagulation tests and biological monitoring of haemostasis according to clinical situations (BIMHO group proposals).	Nougier C, Jeanpierre E, Ternisien C et al.	–	–	外国	Eur J Haematol	参考	無
5.4.17	–	血友病患者に対する止血治療ガイドライン：2019年補遺版　ヘムライブラ（エミシズマブ）使用について	血友病患者に対する止血治療ガイドライン作成委員会	–	–	国内	血栓止血誌	参考	無
5.4.18	–	アレモ皮下注15 mg／アレモ皮下注60 mg／アレモ皮下注150 mg／アレモ皮下注300 mg 添付文書 2025年5月改訂（第3版）	ノボノルディスクファーマ株式会社	–	–	国内	–	参考	無
5.4.19	–	Tissue factor pathway inhibitor: structure-function.	Broze GJ, Girard TJ.	–	–	外国	Front Biosci	参考	無
5.4.20	–	ヒムペブジ皮下注150 mgペン 添付文書 2024年12月作成（第1版）	ファイザー株式会社	–	–	国内	–	参考	無
5.4.21	–	Master protocols to study multiple therapies, multiple diseases, or both.	Woodcock J and LaVange LM.	–	–	外国	N Engl J Med	参考	無
5.4.22	–	Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. Draft Guidance for Industry.	FDA	–	–	外国	–	参考	無
5.4.23	–	エミシズマブ（遺伝子組換え）審査報告書（2018年2月）	医薬品医療機器総合機構	–	–	国内	–	参考	無
5.4.24	–	Phase 3 Trial of Concizumab in Hemophilia with Inhibitors.	Matsushita T, Shapiro A, Abraham A, et al.	–	–	外国	N Engl J Med	参考	無

添付資料番号	報告書番号	タイトル	著者	試験実施期間	試験実施場所	報告書の種類(国内/外国)	掲載誌	評価/参考の別	電子データの提出
5.4.25	－	Efanesoctocog Alfa Prophylaxis for Patients with Severe Hemophilia A.	von Drygalski A, Chowdary P, Kulkarni R, et al.	－	－	外国	N Engl J Med	参考	無