PDL DRUG REVIEW

Proprietary Name: Hympavzi®
Common Name: marstacimab-hncq
PDL Category: Antihemophilic Agents

Comparable Products	Preferred Drug List Status
Hemlibra	Preferred

Pharmacology/Usage: Marstacimab-hncq, the active ingredient of Hympavzi®, is a tissue factor pathway inhibitor (TFPI) antagonist. It is a human monoclonal immunoglobulin G type 1 (IgG1) antibody produced by recombinant DNA technology directed against the Kunitz domain 2 (K2) of TFPI to neutralize TFPI activity and enhance coagulation. TFPI is the main 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.

Marstacimab-hncq causes an increase in total TFPI and downstream biomarkers of thrombin generation such as prothrombin fragments 1+2, peak thrombin, and D-dimer in patients with hemophilia. These changes were observed and persisted over a 7-day period after a single dose and were reversible after treatment discontinuation.

Indication: For routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with:

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

There is no pregnancy category for this medication; however, the risk summary indicates that based on its mechanism of action, Hympavzi® may cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Although there are no data on marstacimab-hncq, monoclonal antibodies can be actively transported across the placenta, and marstacimab-hncq may cause fetal harm. As Hympavzi® may cause fetal harm when administered to a pregnant woman, verify the pregnancy status of females of reproductive potential prior to starting Hympavzi® treatment. In addition, advise female patients of reproductive potential to use effective contraception during treatment with Hympavzi® and for 2 months after the last dose. The safety and efficacy of use have not been established in the pediatric population younger than 12 years old.

Dosage Form: Solution for Injection, available as:

- 150mg/ml in a single-dose prefilled syringe.
- 150mg/ml in a single-dose prefilled pen.

Prior to administration, may be removed from the refrigerator and allowed to warm at room temperature in the carton for 15 to 30 minutes protected from direct sunlight. Do not warm by using a heat source such as hot water or a microwave. After removal from the refrigerator, use within 7 days or discard.

Recommended Dosage: For subcutaneous (SC) use only. It is intended for use under the guidance of a healthcare provider. After proper training in SC injection technique, a patient may self-inject or the patient's caregiver may administer Hympavzi®, if a healthcare provider determines that it is appropriate.

The recommended dosage for adult and pediatric patients 12 years of age and older includes the following: a loading dose of 300mg (two 150mg SC injections; if more than one injection is required to deliver a complete dose, administer each injection at a different injection site) and a maintenance dose of one week after the loading dose initiate 150mg QW SC on the same day each week, at any time of the day.

Consider a dose adjustment to 300mg SC injection weekly in patients weighing ≥50kg when control of bleeding events is judged to be inadequate by the healthcare provider. Safety and efficacy of Hympavzi® at doses above 300mg weekly have not been established.

Administer in the abdomen or thigh. Other injection sites are acceptable if required. Administration in the upper arm (prefilled syringe only) or buttocks (prefilled pen only) should be performed by a caregiver or healthcare professional only. During treatment with Hympavzi®, other medicinal products for SC administration should, preferably, be injected at different anatomical sites.

For patients on a maintenance dose of 150mg and if a dose is missed, administer as soon as possible before the day of the next scheduled dose and then resume usual 150mg SC weekly dosing schedule. If more than 13 days have passed since the last dose was administered, administer a loading dose of 300mg by SC injection followed by a resumption of 150mg SC QW thereafter. For patients on a maintenance dose of 300mg and if one or more doses are missed, administer a dose as soon as possible, and then resume 300mg SC QW dosing schedule.

When changing from prophylactic factor replacement therapy to Hympavzi®: Prior to initiation of Hympavzi®, discontinue treatment with clotting factor concentrates (factor VIII or factor IX concentrates). Hympavzi® can be started at any time after discontinuing clotting factor concentrates. No data are available in patients changing from non-factor-based hemophilia medicinal products to Hympavzi®.

Factor VIII and factor IX products 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 clotting factor concentrates to use, if required, while receiving Hympavzi® prophylaxis, including using the lowest possible effective dose of clotting factor concentrate. Please refer to the full prescribing information for the clotting factor concentrate being used.

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, discontinue Hympavzi® and start management per local standard of care with clotting factor concentrate and measures to manage the risk of venous thrombosis which can be elevated in the perioperative period. Consult the product information for the clotting factor concentrate 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.

There is limited experience with Hympavzi® use in patients with acute severe illness. Reasons to consider temporary dose interruption of Hympavzi® include occurrence of acute severe illness 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.

Verify that females of reproductive potential are not pregnant prior to starting Hympavzi®.

Drug Interactions: 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.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Hympavzi®) in ≥3% of patients. There was no placebo data to compare with in the prescribing information.* The most frequently reported adverse events included injection site reaction (9%), headache (7%), and pruritus (3%).

Hympavzi® is a TFPI antagonist and may increase the risk of thromboembolic complications. Hympavzi® has not been studied in patients with a history of previous thromboembolic events. Interrupt Hympavzi® prophylaxis if diagnostic findings consistent with thromboembolism occur and manage as clinically indicated. If factor VIII or factor IX products are indicated in a patient receiving Hympavzi® prophylaxis, the minimum effective dose of factor VIII or factor IX per the product label is recommended.

Hympavzi® may cause hypersensitivity reactions. If Hympavzi®-treated patients develop a severe hypersensitivity reaction, advise patients to discontinue Hympavzi® and seek immediate emergency treatment.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Pfizer Laboratories Div Pfizer Inc.

Analysis: The efficacy of Hympavzi® was established in adult and pediatric patients (aged 12 years and older and ≥35kg; N=116) with severe hemophilia A without FVIII inhibitors or severe hemophilia B without FIX inhibitors enrolled in a study (BASIS study), which was an open-label, multicenter, two-phase study. Patients with a history of coronary artery disease, venous or arterial thrombosis or ischemic disease were excluded from the study.

After screening, patients entered a 6-month observation phase and were enrolled in 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 who completed the 12-month BASIS study were eligible to enroll in an open-label extension study.

Patients received an initial 300mg loading dose of Hympavzi® followed by maintenance doses of 150mg of Hympavzi® once weekly for 12 months. Fourteen (12%) underwent dose escalation. The mean age of the 116 patients treated with Hympavzi® was 32 years (range 13 to 66), while 19 patients were 12 to less than 18 years of age. All were male, while 56 patients were white. The patient population included 91 with hemophilia A and 25 with hemophilia B. The mean annualized bleeding rates (ABRs) for treated bleeds were 38 and 7.85 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% had 3 or more target joints at study entry. In the routine prophylaxis cohort, 57% 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.

Efficacy results of Hympavzi® prophylaxis compared with on-demand factor-based therapy are presented in the table below, which was adapted from the prescribing information. 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.

Endpoints in the order of testing hierarchy	On-demand factor-based Therapy during 6-month OP (N=33)	Hympavzi® prophylaxis during 12-month ATP (N=33)
Treated Bleeds (primary)		

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)
ABR, model-based	38	3.18
Ratio vs on-demand (OD); p-value	0.084; p<0.0001	
Spontaneous Bleeds, Treated		
ABR, model-based	30.93	2.44
Ratio vs OD; p-value	0.079; p<0.0001	
Joint Bleeds, Treated		
ABR, model-based	32.86	2.83
Ratio vs OD; p-value	0.086; p<0.0001	
Total Bleeds, Treated & Untreated		
ABR, model-based	47.76	7.39
Ratio vs OD; p-value	0.155, p<0.0001	
Target Joint Bleeds, Treated		
ABR, model-based	23.18	1.84
Ratio vs OD; p-value	0.079; p<0.0001	

OP- observational phase; ATP-active treatment phase

The table below presents 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.

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	7.85	5.08
Difference vs routine prophylaxis (RP)	-2.77	
Spontaneous Bleeds, Treated		
ABR, model-based	5.86	3.78
Difference vs RP	-2.09	
Joint Bleeds, Treated		
ABR, model-based	5.66	4.13
Difference vs RP	-1.53	

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)
Total Bleeds, Treated & Untreated		
ABR, model-based	8.84	5.97
Difference vs RP	-2.87	
Target Joint Bleeds, Treated		
ABR, model-based	3.36	2.51
Difference vs RP	-0.86	

OP- observational phase; ATP-active treatment phase

Place in Therapy: Hympavzi® is a tissue factor pathway inhibitor (TFPI) antagonist indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or hemophilia B (congenital factor IX deficiency) without factor IX inhibitors. It is for subcutaneous use only and may be self-injected by the patient or the patient's caregiver may administer after proper training in subcutaneous injection technique. After a loading dose, the maintenance dose is to be administered once every week. The efficacy of Hympavzi® was established in adult and pediatric patients with severe hemophilia A without FVIII inhibitors or severe hemophilia B without FIX inhibitors in an open-label, two-phase study. 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. 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.

Summary

There is some evidence at this time in a phase 3 study to suggest that Hympavzi® during a 12-month active treatment phase may be more effective than on-demand factor-based therapy during a 6-month observational phase for treated bleeds (primary), spontaneous bleeds (treated), joint bleeds (treated), total bleeds (treated & untreated), and target joint bleeds (treated); however, there is no evidence at this time to support that Hympavzi® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Hympavzi® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Hympavzi® [package insert]. New York, NY: Pfizer Inc; 2024.

Prepared By: Iowa Medicaid Date: 02/17/2025