Hympavzi®

Patient safety information Card

The marketing of Hympavzi is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment.

Please explain to the patient the need to review the card before starting treatment.

1 NAME OF THE MEDICINAL PRODUCT

Hympavzi

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Inactive ingredients with known effect
Hympavzi contains 0.2 mg polysorbate 80 in each mL of solution.
For the full list of inactive ingredients, see section 11.

3 THERAPEUITC INDICATIONS

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

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

4 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.

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

Treatment of acute severe illness should be managed per local standard of care, and continued treatment with Hympavzi in this situation should be weighed against the potential risks involved. Additional monitoring for adverse reactions and the development of thromboembolism may be warranted in these patients when marstacimab is administered. Hympavzi should be temporarily interrupted if clinical symptoms, imaging, and/or laboratory findings consistent with thrombotic events occur, and managed as clinically indicated. Hympavzi therapy may be resumed once the patient has clinically recovered at the clinical judgement of the healthcare provider (see Missed dose section below).

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

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

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

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

Special populations

Hepatic impairment
No dose adjustments are recommended in patients with mild hepatic impairment (see section 12.3). 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 12.3). 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 12.3).

Paediatric population

Hympavzi should not be used in children less than 1 year of age because of potential safety issues. The safety and efficacy of marstacimab in paediatric patients < 12 years of age have not yet been established. The safety and efficacy of marstacimab in adolescents with a body weight < 35 kg have not been established. No data are available.

Management in the perioperative setting

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

For major surgery, it is recommended to discontinue Hympavzi 6 to 12 days prior and initiate management per local standard of care with clotting factor concentrate and measures to manage the risk of venous thrombosis which can be elevated in the perioperative period. The product information for the clotting factor concentrate should be consulted for dose guidelines in patients with haemophilia undergoing major surgery. Resumption of Hympavzi therapy should take into account the overall clinical status of the patient, including the presence of post-surgical thromboembolic risk factors, use of other haemostatic products and other concomitant medicinal products (see Missed dose section above).

Method of administration

Hympavzi is for subcutaneous use only.

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

Prior to subcutaneous administration, Hympavzi may be removed from the refrigerator and allowed to warm at room temperature in the carton for about 15 to 30 minutes away from direct sunlight. 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 buttocks 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 the 'Instructions for Use' provided at the end of the package leaflet.

5 DOSAGE FORMS AND STRENGTHS

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

Prefilled Pen
- Injection: 150 mg/mL in a single-dose prefilled pen

6 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the inactive ingredients listed in section 11.

7 WARNINGS AND PRECAUTIONS

7.1 Thromboembolic Events

HYMPAVZI is a tissue factor pathway inhibitor (TFPI) antagonist, and may increase the risk of thromboembolic complications.

HYMPAVZI has not been studied in patients with a history of previous thromboembolic events *[see Clinical Studies (14.1)]*. 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 according to the product label is recommended.

Inactive ingredients

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'.

7.2 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.

7.3 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 (10.1, 10.3)]*.

Driving and using machines

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

8 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Thromboembolic Events *[see Warnings and Precautions (7.1)]*
- Hypersensitivity *[see Warnings and Precautions (7.2)]*

8.1 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 adolescent and adult patients with severe hemophilia A or B without inhibitors (coagulation factor activity <1%) enrolled in the BASIS study *[see Clinical Studies (14.1)]*. Patients (N = 116) received HYMPAVZI prophylaxis 300 mg loading dose followed by 150 mg every week starting at Day 8 administered subcutaneously. Among patients receiving HYMPAVZI, 97% were exposed for 6 months or longer and 75% were exposed for at least 1 year.

A serious adverse reaction of peripheral swelling occurred in one patient.

Table 1 summarizes the adverse reactions reported in ≥3% of patients who received HYMPAVZI prophylaxis.

Table 1. Adverse Reactions Reported in ≥3% of Patients Treated with HYMPAVZI*

Adverse Reaction	**Number of Patients n (%) (N = 116)**
Injection site reaction	11 (9)
Headache	8 (7)
Pruritus	4 (3)

*During BASIS trial 12-month active treatment phase

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

9 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 therapy.

10 USE IN SPECIFIC POPULATIONS

10.1 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, monoclonal antibodies can be actively transported across the placenta, and marstacimab 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.

10.2 Lactation

Risk Summary
There are no data on the presence of marstacimab 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 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.

10.3 Females and Males of Reproductive Potential
HYMPAVZI may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (10.1)]*.

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.

10.4 Pediatric Use
The safety and effectiveness of HYMPAVZI to prevent or reduce the frequency of bleeding episodes in hemophilia A or B without inhibitors have been established in pediatric patients aged 12 years and older *[see Clinical Studies (14.1)]*. Use of HYMPAVZI for this indication is supported by evidence from an open-label, multi-center phase 3 study in 19 adolescents and 97 adults with hemophilia without inhibitors.

The safety and effectiveness of HYMPAVZI have not been established in pediatric patients younger than 12 years old.

10.5 Geriatric Use
One patient 65 years of age and older was enrolled in the clinical studies for hemophilia A or B without

inhibitors *[see Clinical Studies (14.1)]*. Clinical studies of HYMPAVZI did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

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

HYMPAVZI (marstacimab) injection is supplied as a sterile, preservative-free solution for subcutaneous administration. The drug product is supplied as a single-dose 150 mg/mL prefilled pen. The solution of marstacimab is clear and colorless to light yellow with a pH of 5.8.

Each 150 mg/mL prefilled pen delivers 1 mL of HYMPAVZI. Each 1 mL of HYMPAVZI contains 150 mg of marstacimab, and the inactive ingredients sucrose, L-histidine monohydrochloride, L-histidine, polysorbate 80, disodium edetate and Water for Injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Marstacimab 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

Marstacimab causes an increase in total TFPI (comprised of free TFPI and TFPI bound to marstacimab) 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 following a single subcutaneous dose and were reversible after treatment discontinuation.

12.3 Pharmacokinetics

Estimated mean marstacimab $C_{min,ss}$, $C_{max,ss}$, and $C_{avg,ss}$ for adults and adolescents weighing at least 35 kg following marstacimab 150 mg subcutaneous once-weekly administration are shown in Table 2.
Marstacimab area under the plasma concentration-time curve (AUC) and 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).

Mean steady-state accumulation ratio for marstacimab is approximately 4 to 5. Marstacimab steady-state concentrations are achieved by approximately 60 days (8^{th} or 9^{th} subcutaneous dose) when administered once weekly.

Table 2. Steady-State Marstacimab Plasma Concentrations Following Once-Weekly Subcutaneous Administration of 150 mg (with a Loading Dose of 300 mg Subcutaneous)

Parameter	Adults	Adolescents
$C_{min,ss}$ (mcg/mL)	13.7 (90.4%)	27.3 (53.2%)
$C_{max,ss}$ (mcg/mL)	17.9 (77.5%)	34.7 (48.5%)

$C_{avg,ss}$ (mcg/mL)	16.5 (81.2%)	32.1 (49.5%)

- Data are presented as arithmetic mean (%CV).
- $C_{min,ss}$ = minimum plasma concentration at steady state; $C_{max,ss}$ = maximum plasma concentration at steady state; $C_{avg,ss}$ = average plasma concentration at steady state.

Absorption

Bioavailability of marstacimab following subcutaneous administration is approximately 71%. Median Tmax ranges from 23 to 59 hours following multiple subcutaneous administrations of marstacimab to patients with hemophilia. No clinically significant differences were seen in marstacimab bioavailability when administered subcutaneously in the arm, thigh or abdomen.

Distribution

Marstacimab steady-state apparent volume of distribution is 8.6 L in patients with hemophilia.

Elimination

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

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 10 days).

Metabolism

Marstacimab 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 were observed based on race, hemophilia type (A and B), mild renal impairment (eGFR of 60 to 89 mL/min/1.73 m^2), and mild hepatic impairment (total bilirubin >1× to ≤1.5× ULN). 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 pharmacokinetics are unknown.

Body Weight

Body weight was a significant covariate impacting the pharmacokinetics of marstacimab.
Marstacimab exposures over the body weight range of 35 to 120 kg show a trend for increase in exposure with decrease in body weight. However, dose adjustment based on body weight is not required.

Pediatric Patients

Marstacimab clearance (CL) was 29% lower in adolescents (12 to <18 years of age) compared to adults (18 years and older). No clinically significant difference in adolescent marstacimab CL (L/hr/kg) compared to adults was observed after adjusting for body weight.

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 or of other marstacimab products.

During the 12-month active treatment phase in the BASIS study, 23 of the 116 (19.8%) ADA-evaluable marstacimab-treated patients developed ADAs. Among the 23 patients who tested positive for ADA, 6 patients (26%) developed neutralizing antibodies (NAbs) against marstacimab. Subjects who received marstacimab and developed anti-marstacimab antibodies had reduced marstacimab steady-state concentrations, geometric mean decrease in the range of 24% to 50%, compared to those who did not develop anti-marstacimab antibodies through the course of the treatment period.

There was no identified clinically significant effect of ADAs, including NAbs, on safety or efficacy of marstacimab over the treatment duration of 12 months.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to assess marstacimab for the potential for carcinogenicity or mutagenicity. Marstacimab 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 without FVIII Inhibitors or Hemophilia B without FIX Inhibitors

The efficacy of HYMPAVZI was established in 116 adult and pediatric patients (aged 12 years and older and ≥35 kg) with severe hemophilia A without FVIII inhibitors or severe hemophilia B without FIX inhibitors enrolled in the BASIS study (NCT03938792), an open-label, multi-center, two-phase study. Severe hemophilia is defined as factor activity less than 1%. 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 who completed the 12-month BASIS study were eligible to enroll in an open-label extension study (NCT05145127).

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 breakthrough bleeds. Fourteen (12%) underwent dose escalation.

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.

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 <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 without Factor VIII or Factor IX Inhibitors

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

- 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 FVIII or FIX; Total bleeds = bleeds treated and not treated with FVIII or FIX

- ABR = Annualized Bleeding Rate; CI = Confidence Interval; OD = On-Demand; OP = Observational Phase; ATP = Active Treatment Phase

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 without Factor VIII or Factor IX Inhibitors

Endpoints in the Order of Testing Hierarchy	Routine Factor-Based Prophylaxis During 6-Month OP (N = 83)	HYMPAVZI Prophylaxis During 12-Month ATP (N = 83)
Treated Bleeds (Primary)		
ABR, model-based (95% CI)	7.85 (5.09, 10.61)	5.08 (3.40, 6.77)
Difference vs. RP (95% CI)	−2.77 (−5.37, −0.16)	
Spontaneous Bleeds, Treated		
ABR, model-based (95% CI)	5.86 (3.54, 8.19)	3.78 (2.25, 5.31)
Difference vs. RP (95% CI)	−2.09 (−4.23, 0.06)	
Joint Bleeds, Treated		
ABR, model-based (95% CI)	5.66 (3.33, 7.98)	4.13 (2.59, 5.67)
Difference vs. RP (95% CI)	−1.53 (−3.70, 0.64)	
Total Bleeds, Treated & Untreated		
ABR, model-based (95% CI)	8.84 (5.97, 11.72)	5.97 (4.13, 7.81)
Difference vs. RP (95% CI)	−2.87 (−5.61, −0.12)	
Target Joint Bleeds, Treated		
ABR, model-based (95% CI)	3.36 (1.59, 5.14)	2.51 (1.25, 3.76)
Difference vs. RP (95% CI)	−0.86 (−2.41, 0.70)	

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

HYMPAVZI (marstacimab) injection is a sterile, preservative-free, colorless to light yellow solution, practically free from visible particles, available as a 150 mg/mL single-dose prefilled pen for subcutaneous administration.

Prefilled Pen

Each carton contains one 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 Shelf life

The expiry date of the product is indicated on the packaging materials.

16.3 Recommended Storage and Handling

- Store in a refrigerator (2 °C - 8 °C) in the original carton in order to protect from light.
- Do not freeze.
- Hympavzi 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). Once stored at room temperature, Hympavzi must not be returned to refrigerated storage and it must be used or discarded after 7 days.
- Do not shake.

LICENSE HOLDER

Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya 4672509.

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