Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM044.0225	**HEMATOLOGICAL AGENTS** **HYMPAVZI™** (marstacimab-hncq pen)
Effective Date: 4/1/2025	**Review/Revised Date**:
Original Effective Date: 04/25	**P&T Committee Meeting Date**: 02/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For initial authorization, must meet all the following criteria:
1. Use is for routine prophylaxis to prevent or reduce the frequency of bleeding episodes
2. Must meet criteria for one of the following (Hemophilia A **OR** Hemophilia B):
    a. Diagnosis of severe hemophilia A (congenital factor VIII deficiency) defined as pre-treatment factor VIII level less than 1 IU/dL or less than 1% of normal factor levels
    b. Diagnosis of moderately severe to severe hemophilia B (congenital factor IX deficiency) defined as pre-treatment factor IX level less than 2 IU/dL or less than or equal to 2% of normal factor levels
3. Patient does not have inhibitors defined as one of the following:
    a. For Hemophilia A: factor VIII inhibitor titer less than 0.6 Bethesda units (BU) per mL
    b. For Hemophilia B: factor IX inhibitor titer less than 0.6 Bethesda units (BU) per mL
4. Weigh 35 kg or more at treatment initiation
5. Dose and frequency must be in accordance with FDA-approved labeling

For reauthorization:

1. Documentation of response to therapy indicating a beneficial response (such as a reduction in bleeding events, in the severity of bleeding episodes, in the number of bleeding events that required treatment, and/or in the number of spontaneous bleeds)
2. Dose and frequency must be in accordance with FDA-approved labeling

EXCLUSION CRITERIA:
Use with other prophylactic therapies (such as emicizumab-kxwh).

AGE RESTRICTIONS:
Age must be appropriate based on FDA-approved indication.

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a hematologist.

COVERAGE DURATION:
Authorization and reauthorization will be approved for one year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Marstacimab-hncq (Hympavzi™) is a human monoclonal immunoglobulin G1 (IgG1) antibody directed against the Kunitz domain 2 (K2) of tissue factor pathway inhibitor (TFPI) to neutralize TFPI activity and enhance coagulation. TFPI blocks early phases of coagulation by inhibiting activated factor VII (FVIIa) and activated factor X (FXa). Marstacimab may be self-administered or caregiver-administered after proper training by healthcare provider. The recommended dose for adult and pediatric patients 12 years of age and older is as follows:

- Loading dose: 300 mg (two 150 mg subcutaneous injections).

- Maintenance dosing: One week after the loading dose, initiate maintenance dosing of 150 mg once every week on the same day by subcutaneous injection.
- Dose adjustment: 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 provider.

FDA APPROVED INDICATIONS:
Marstacimab-hncq (Hympavzi™) is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults 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

POSITION STATEMENT:
- Hemophilia is an X-linked recessive genetic disorder caused by mutations in the genes that encode coagulation factors, leading to deficiencies in the proteins necessary for normal blood clotting. Specifically, hemophilia A is characterized by a deficiency in factor VIII (FVIII), while hemophilia B is caused by a deficiency in factor IX (FIX). Hemophilia primarily affects males, and it is estimated that between 30,000 and 33,000 males in the United States live with hemophilia A or B, with approximately 76% of them having hemophilia A. About 60% of these individuals have the severe form of the disorder. Individuals with hemophilia, particularly those with severe disease, are at risk for life-threatening bleeding, including intracranial hemorrhages. While bleeding often occurs following an injury, individuals with hemophilia may also experience frequent spontaneous bleeding episodes, most commonly into the joints or muscles.
- The severity of the disease is determined by the level of clotting factor in the blood and is typically classified as:
    - Mild disease: 5–40 IU/dL or 5%–40% of normal factor levels
    - Moderate disease: 1–5 IU/dL or 1%–5% of normal factor levels
    - Severe disease: <1 IU/dL or <1% of normal factor levels[4-6]
- Prophylaxis with plasma-derived or recombinant standard half-life factor, extended half-life factor, or non-factor replacement emicizumab (Hemlibra®) is the standard of care for preventing bleeding in patients with severe hemophilia. Treatment is typically initiated before the age of 3. Although all prophylaxis products effectively prevent bleeding, they differ in patient responses, safety profiles (including the risk of inhibitor development), costs, and product characteristics (such as half-life and effects on monitoring). The choice of prophylaxis is a team-based decision that considers the patient's specific circumstances and needs, with the primary goal of preventing bleeding.[9-11]

Clinical Trials:[7,8]

BASIS (NCT03938792- unpublished)

- Phase 3, open-label, multicenter, two-phase study consisted of a 6-month observational phase (OP), during which participants were enrolled in two cohorts. One cohort, the on-demand (OD) treatment group, received factor replacement therapy as needed in response to bleeding symptoms, while the other cohort, the prior routine prophylactic (RP) treatment group, received scheduled or routine factor replacement therapy to prevent bleeds. This was followed by a 12-month active treatment phase (ATP) of marstacimab prophylaxis. Participants were all adult and pediatric males (N=116) 13 to 66 years old, weighing at least 35 kilograms, and with a diagnosis of severe hemophilia A (FVIII levels <1% of normal) without FVIII inhibitors or moderately severe to severe hemophilia B (FIX levels ≤2%) without FIX inhibitors.
- The primary endpoint was a non-inferiority test of annualized bleeding rate (ABR) during the 12-month ATP phase of marstacimab compared with the ABR of the OD and RP cohorts during the OP. Key secondary endpoints include the incidence of total bleeds, spontaneous bleeds, joint bleeds, and target joint bleed.
- Efficacy: The mean ABR for treated bleeds were 38 [95% CI: 31.03, 46.54] in the OD cohort and 7.85 [95% CI: 5.09, 10.61] in RP cohort during the OP. Following marstacimab treatment in the ATP, mean ABRs for treated bleeds were 3.18 [95% CI: 2.09, 4.85] in the OD cohort and 5.08 [95% CI: 3.40, 6.77] in the RP cohort, reflecting a 91.6% and 35.2% reduction over a 12-month ATP, respectively.
- Secondary endpoints:
    - Marstacimab prophylaxis demonstrated superiority over OD factor-based therapy and noninferiority to RP factor-based therapy in reducing spontaneous bleeds, joint bleeds, total bleeds, and target joint bleeds.

Comparison of ABRs with Marstacimab Prophylaxis vs Previous OD or RP

Marstacimab Prophylaxis vs. OD Factor-Based Therapy		**Marstacimab Prophylaxis vs. Previous Factor-Based RP**	
OD Factor-Based Therapy During 6-Month OP (N=33)	Marstacimab Prophylaxis, 12-Month ATP (N=33)	Factor-Based RP During 6-Month OP (N=83)	Marstacimab Prophylaxis, 12-Month ATP (N=83)
Treated Bleeds (Primary endpoint)			
38.00 (31.03, 46.54)	3.18 (2.09, 4.85)	7.85 (5.09, 10.61)	5.08 (3.40, 6.77)
Ratio vs. OD (95% CI), *P*-value		**Difference vs. RP (95% CI)**	
0.084 (0.059, 0.119), <0.0001		−2.77 (−5.37, −0.16)	
Spontaneous Bleeds, Treated			

30.93 (24.12, 39.67)	2.44 (1.61, 3.69)	5.86 (3.54, 8.19)	3.78 (2.25, 5.31)
Ratio vs. OD (95% CI), *P*-value		**Difference vs. RP (95% CI)**	
0.079 (0.054, 0.114), <0.0001		−2.09 (−4.23, 0.06)	
Joint Bleeds, Treated			
32.86 (26.15, 41.29)	2.83 (1.81, 4.44)	5.66 (3.33, 7.98)	4.13 (2.59, 5.67)
Ratio vs. OD (95% CI), *P*-value		**Difference vs. RP (95% CI)**	
0.086 (0.059, 0.125), <0.0001		−1.53 (−3.70, 0.64)	
Total Bleeds, Treated and Untreated			
47.76 (39.60, 57.60)	7.39 (5.08, 10.74)	8.84 (5.97, 11.72)	5.97 (4.13, 7.81)
Ratio vs. OD (95% CI), *P*-value		**Difference vs. RP (95% CI)**	
0.155 (0.116, 0.207), <0.0001		−2.87 (−5.61, −0.12)	
Target Joint Bleeds, Treated			
23.18 (17.20, 31.24)	1.84 (1.06, 3.17)	3.36 (1.59, 5.14)	2.51 (1.25, 3.76)
Ratio vs. OD (95% CI), *P*-value		**Difference vs. RP (95% CI)**	
0.079 (0.051, 0.124), <0.0001		−0.86 (−2.41, 0.70)	

- Adverse reactions in >3% of patients treated with marstacimab: injection site reaction (N=11, 9%), headache (N=8, 7%), and pruritus (N=4, 3%).
- There were no reported discontinuations due to adverse reactions, and no deaths or thrombotic or embolic events were observed.

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