Hympavzi®
(marstacimab-hncq)

Date of Origin: 05/02025 **Last Review Date: 02/11/2026** **Effective Date: 05/07/2025**

Dates Reviewed: 02/25/2026

Developed By: Medical Criteria Committee

I. Length of Authorization

A. Authorization is valid for 12 months and may be renewed.

II. Dosing Limits

A. Max Units (per dose and over time) [Medical Benefit]:
- 600 billable units every week

III. Initial Evaluation

I. **Marstacimab (Hympavzi)** may be considered medically necessary when the following criteria are met:
   A. Member is 12 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist; **AND**
   C. Medication will not be used in combination with other agents for routine prophylaxis [e.g., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]; **AND**
   D. Marstacimab (Hympavzi) will be used as routine prophylaxis to reduce the frequency of bleeding episodes; **AND**
   E. Clinical documentation confirming that the member does not have history of inhibitors [i.e., documented high-titer inhibitor (≥5 BU/mL)]; **AND**
   F. A diagnosis of one of the following:
      i. **Hemophilia A**; **AND**
         1. Member has severe hemophilia A (defined as factor VIII level of <1%); **OR**
            a. Member has had two or more documented episodes of spontaneous bleeding; **AND**
         2. Clinical documentation that prior prophylaxis with factor VIII (e.g., Advate, Eloctate, Nuwiq, etc.) was ineffective for prevention of bleeding episodes; **AND**
         3. Clinical documentation of intolerance or contraindication to emicizumab-kxwh (Hemlibra); **OR**
      ii. **Hemophilia B**; **AND**
         1. Member has moderate to severe hemophilia B (defined as factor IX level of less than or equal to 5%); **OR**
            a. Member has had two or more documented episode of spontaneous bleeding; **AND**
         2. Clinical documentation that prior prophylaxis with factor IX (e.g., BeneFIX, Idelvion, etc.) was ineffective for the prevention of bleeding episodes

II. Marstacimab (Hympavzi) is considered investigational when used for all other conditions, including but not limited to:

A. Marstacimab (Hympavzi) used in combination with other agents for routine prophylaxis [e.g., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]
B. Pediatric patients <12 years of age with hemophilia A or B
C. Hemophilia A with inhibitors
D. Hemophilia B with inhibitors
E. Mild-to-moderate hemophilia A (Factor activity level ≥ 1% of normal and < 40% of normal (≥ 0.01 and < 0.40 IU/mL)
F. Mild hemophilia B (Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL)
G. Von Willebrand disease

IV. Renewal Evaluation

A. Member has exhibited improvement or stability of disease symptoms (e.g., decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline); **AND**
B. Medication will not be used in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]; **AND**
C. If the request is for marstacimab (Hympavzi) dose escalation to 300 mg per week:
    i. Member has demonstrated an initial response to therapy at a dose of 150 mg weekly (i.e., decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline); **AND**
    ii. Current weight is greater than or equal to 50 kg; **AND**
    iii. Member has experienced two or more breakthrough bleeds while on marstacimab (Hympavzi) 150 mg weekly; **AND**
    iv. Dose escalation will not exceed 300 mg per week.

V. Supporting Evidence

A. Marstacimab (Hympavzi) is a tissue factor pathway inhibitor (TFPI) antagonist FDA-approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients 12 years of age and older with hemophilia A and B without inhibitors. Tissue factor pathway inhibitor (TFPI) is an anticoagulation protein that regulates the extrinsic coagulation cascade by inactivating the protease functions of FXa/FVIIa/TF complex. When TFPI activity is blocked, the extrinsic coagulation cascade continues to work without requiring amplification by FVIII/FIX whose normal plasma levels are reduced in hemophilia.
B. The efficacy and safety of marstacimab (Hympavzi) has not been studied in a pediatric population less than 12 years of age. Current FDA approval is limited to those 12 years of age and older.
C. Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX) are X-linked inherited coagulation factor deficiencies that result in lifelong bleeding disorders. The availability of factor replacement products has dramatically improved care for those with hemophilia A and B. The severity of an individual's hemophilia is determined by the amount of clotting factor present. Plasma levels of FVIII or FIX < 40% are indicative of hemophilia; however, hemophilia A and B are classified moderate when factor levels are 1% to < 5%, and severe when factor levels are < 1%. Joint bleeds are the most frequent bleeding experienced by people with hemophilia of all severities (70-80%) which can lead to deformity, arthropathy, and irreversible joint damage leading to decreased mobility. Given the

complexities of diagnosis and treatment of hemophilia A and B, supervision of treatment by a hematologist is required.

D. The World Federation of Hemophilia (WFH) guidelines recommend use of agents for both bleeding prophylaxis and control of acute breakthrough bleeds. Therapy recommendations are not sequential, but rather cite the need for individualized care considering a patient's bleeding phenotype, joint status, pharmacokinetic profile, and preference. Medications include factor replacement with clotting factor concentrates (CFCs) (i.e., standard half-life (SHLs) for FVIII for hemophilia A and FIX for hemophilia B), long-acting CFCs (i.e., extended half-life (EHLs)), non-factor, and gene therapies. The frequency of injections varies but overall injection burden is high. Guidelines have not been updated to include marstacimab (Hympavzi).
E. There are varying severities of hemophilia A and B depending on the level of factor produced by the patient, these are divided into the following per the International Society on Thrombosis and Hemostasis (ISTH):
    - Severe: <1% factor activity (<0.01 IU/mL)
    - Moderate: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
    - Mild: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL)
F. There is a lack of strong scientific evidence from randomized controlled trials supporting the efficacy and safety of multiple agents for routine prophylaxis used in combination. Therefore, use of marstacimab (Hympavzi) in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.] is not allowable per policy. There is a lack of head-to-head trials showing superior safety or efficacy comparing marstacimab (Hympavzi) to other prophylactic agents for the treatment of hemophilia A or B. Given the known safety, established efficacy, and cost-effectiveness of these therapies, prior prophylaxis with factor VIII and emicizumab-kxwh (Hemlibra), or factor IX remains the preferred specialty agents by this plan due to efficacy, safety, and cost. Marstacimab (Hympavzi) is specifically more costly than other agents, despite not having any evidence of improved clinical efficacy or safety.
G. Marstacimab (Hympavzi) was studied in the BASIS trial, a Phase 3, one-way, crossover, open-label, study in adolescent and adult participants with severe hemophilia A (coagulation FVIII activity < 1%) or moderate to severe hemophilia B (coagulation FIX activity ≤ 2%). Patients in the routine FVIII/FIX prophylaxis (RP) group were required to have demonstrated at least 80% compliance while participants in the on-demand (OD) treatment group were required to have ≥6 acute bleeding episodes requiring factor infusion during the six months prior to enrollment. Those using a bypassing agent, non-coagulation non-factor replacement therapy, or any previous gene therapies were excluded. The primary outcome was reduction in the annualized bleeding rate (ABR) for treated patients compared to their own current standard treatment versus a 12-month active phase of participants receiving prophylaxis treatment with marstacimab (Hympavzi). Among the 116 patients treated with marstacimab (Hympavzi), the mean age was 32 years (range 13 to 66), 91 (78%) with hemophilia A and 25 (22%) with hemophilia B. All patients in the OD cohort had one or more target joints at study entry and 36% had three or more target joints at study entry. Whereas in the RP cohort, 57% of the patients had one or more target joints at study entry and 16% had three or more target joints at study entry.
H. The results of the BASIS clinical trial showed that marstacimab (Hympavzi) prophylaxis demonstrated statistical superiority over OD treatment and noninferiority over RP treatment with factor-based therapies, as measured by the ABR of bleed events. It is unknown how marstacimab (Hympavzi) compared to prophylaxis with bypassing or subcutaneous non-factor therapies [e.g., (emicizumab-kxwh (Hemlibra)] as participants treated with these agents were excluded under the protocol. The bias of an open-label treatment design may be mitigated as bleed events are objective

and each participant went through the observation phase with their own standard therapy before crossing over to marstacimab (Hympavzi). While not statistically evaluated in the hierarchical testing procedure, marstacimab (Hympavzi) numerically improved Hemophilia Joint Health Scores; however, the minimal clinically important difference was not achieved. Long term safety and efficacy is still relatively unknown and will be realized in the real-world setting. Therefore, the quality of evidence is considered moderate.

I. Marstacimab (Hympavzi) was not directly compared with to prophylaxis with bypassing or subcutaneous non-factor therapies for the treatment of hemophilia A or B. Balancing long-term safety data, efficacy, and costs of alternative therapies compared to marstacimab (Hympavzi), treatment with prior prophylactic factor therapies and emicizumab-kxwh (Hemlibra), when applicable, is required.

J. For individuals who have had more than one bleeding episode (e.g., two or more bleeds into a target joint, evidence of joint disease by physical exam or radiography), prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level. Use of on demand therapy in those with mild-to-moderate disease with less than two instances of spontaneous bleeding is considered clinically appropriate for the management of hemophilia.

K. Dose escalation from a starting dose of 150 mg to 300 mg of marstacimab (Hympavzi) once weekly was permitted in the clinical trial setting and is an FDA approved dosing regimen. Those participants weighing ≥50 kg and experiencing two or more breakthrough bleeds after undergoing six months of treatment were eligible for dose escalation. While use of prophylactic therapies reduces the number of bleed events patients with hemophilia will still experience bleeds. Therefore, dose escalation should be considered for those most at risk of bleed events.

Investigational or Not Medically Necessary Uses

I. Marstacimab (Hympavzi) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Marstacimab (Hympavzi) used in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]
      i. Use of dual therapies for routine prophylaxis have not been evaluated for safety and efficacy.
   B. Pediatric patients <12 years of age with hemophilia A or B
      i. Clinical trial data is currently limited to adult and adolescent patients 12 years of age and older. BASIS KIDS, an open-label study investigating the safety and efficacy of marstacimab in children 1 to <18 years of age with severe hemophilia A or moderately severe to severe hemophilia B with or without inhibitors is still ongoing.
   C. Hemophilia A & B with inhibitors
      i. The published efficacy data from the BASIS trial only consisted of the without inhibitor cohort. Clinical trials are still ongoing to determine the safety and efficacy of marstacimab (Hympavzi) in those without inhibitors. The inhibitor cohort of the BASIS trial is ongoing, with results expected in the third quarter of 2025.
   D. Mild-to-moderate hemophilia A (Factor activity level ≥ 1% of normal and < 40% of normal (≥ 0.01 and < 0.40 IU/mL) and Mild hemophilia B (Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL)
      i. Data from the BASIS clinical trial program is limited to those with severe hemophilia A (defined as factor VIII level of <1%) or moderate to severe hemophilia B (defined as factor

IX level of less than or equal to 2% in clinical trials). Use for the treatment of mild to moderate disease has not been evaluated in clinical trials.

VI. Dosage/Administration

Indication	Dose
Routine Prophylaxis in Congenital Hemophilia A or Hemophilia B without inhibitor	**Loading Dose:** • 300 mg (two 150 mg subcutaneous injections) **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 Escalation During Treatment:** Consider a dose adjustment to 300 mg subcutaneous injection weekly in patients weighing greater than or equal to 50 kg when control of bleeding events is judged to be inadequate by the healthcare provider. Safety and efficacy at doses above 300 mg weekly have not been established
1 billing unit = 0.5 mg	

VII. Billing Code/Availability Information

- Jcode:
  - J7172 – injection, Hympavzi, marstacimab-hncq, 0.5mg; 1 billable unit = 0.5mg
- NDC:
  - Hympavzi, marstacimab-hncq 150 mg/mL prefilled pen: 0069-2151-01
  - Hympavzi, marstacimab-hncq 150/1.5 mL prefilled syringe: 0059-1510-01

VII. References

1. Hympavzi. Package Insert. Pfizer Inc; October 2024.
2. Matino D, Acharya S, Palladino A, et al. Efficacy and safety of the anti-tissue factor pathway inhibitor marstacimab in participants with severe hemophilia without inhibitors: results from the phase 3 BASIS trial. *Blood*. 2023;142 (suppl 1):abstr 285. https://doi.org/10.1182/blood-2023-181263
3. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020: 26(Suppl 6): 1-158.
4. Hympavzi product dossier. Pfizer. October 17, 2024.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
D66	Hemophilia A (congenital factor VIII deficiency) with or without FVIII inhibitors
D67	Hemophilia B (congenital factor IX deficiency) with or without FIX inhibitors