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Subject: Subcutaneous Prophylactic Therapy for Hemophilia (Non-Clotting Factor)

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DESCRIPTION:

Hemophilia is an X-linked recessive genetic disorder that primarily affects approximately 33,000 males in the United States, although in rare cases, females can have the disorder. It is caused by mutations in the genes encoding coagulation factors, which causes bleeding into soft tissue, joints, and internal organs. Hemophilia can also cause severe bleeding and death in traumatic incidents. Treatments for hemophilia are typically designed to replace the missing coagulation factor. Generally, higher levels of coagulation factors are associated with improved clinical outcomes and are required for patients with joint-affected disease to decrease the risk of bleeds and reduce long-term complications from bleeding.

There are two main types of hemophilia: hemophilia A is caused by a deficiency in factor VIII (FVIII), and hemophilia B is caused by a deficiency in factor IX (FIX). 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

Depending on severity and bleed frequency, patients with hemophilia A may receive prophylaxis with self-administered intravenously (IV) infused FVIII products or emicizumab-kxwh (Hemlibra), a subcutaneously (SQ) administered bispecific antibody designed to mimic the function of FVIII. Patients with hemophilia B may receive prophylaxis with self-administered IV infused FIX products. In 2024, the FDA approved two new SQ products for routine prophylaxis to prevent or reduce bleeding events in patients with hemophilia A or B.

Concizumab (Alhemo)

Concizumab (Alhemo), a tissue factor pathway inhibitor (TFPI) antagonist, was approved by the U.S. Food and Drug Administration (FDA) in 2024 to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ≥12 years of age with hemophilia A (congenital factor VIII [FVIII] deficiency) with FVIII inhibitors or hemophilia B (congenital factor IX [FIX] deficiency) with FIX inhibitors. Concizumab is the second TFPI approved for the treatment of hemophilia A and B. Unlike traditional hemophilia treatments that replace clotting factors, concizumab reduces the amount and activity of naturally occurring TFPI. This increases the amount of thrombin that is generated resulting in the prevention of or a reduction in bleeding episodes. Concizumab is administered as a once-daily subcutaneous injection

The safety and efficacy of concizumab to prevent or reduce the frequency of bleeding episodes was evaluated in adult and pediatric patients 12 years of age and older (n=133) with hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors or hemophilia B with inhibitors in the randomized clinical trial (explorer7, NCT04083781). Patients were randomized to receive concizumab prophylaxis for 32 weeks or more (n=33) or on-demand treatment (no prophylaxis) for 24 weeks or more (n=19); these groups were included in the primary analysis. Other patients in the trial included a group who previously received concizumab in explorer4 and was transferred to concizumab prophylaxis (n=21) and a group who was previously receiving bypassing agents and was transferred to concizumab prophylaxis (n=60; these groups were not included in primary outcome measures).

The primary endpoint of estimated mean annualized bleeding rate (ABR) for treated and spontaneous bleeding episodes was 1.7 for concizumab (range, 1 to 2.9) and 11.8 for no prophylaxis (range, 7 to 19.9). This represents an 86% reduction in ABR in patients randomized to receive concizumab prophylaxis compared to no prophylaxis (ABR ratio 0.14, 95% CI, 0.07 to 0.29). The overall median ABR was zero for treated spontaneous and traumatic bleeds compared with 9.8 ABR in patients with no prophylaxis. As a supportive secondary efficacy endpoint, 64% of the patients randomized to receive concizumab prophylaxis treatment experienced zero treated spontaneous and traumatic bleeds during the first 24 weeks of treatment versus 11% with no prophylaxis.

In the safety analysis of 127 patients, 63% experienced an adverse event. The most common adverse events were arthralgia (10%), injection site erythema (7%), and upper respiratory tract infection (6%). Serious adverse events occurred in 11% of patients who received concizumab (vs 16% in the on-demand no prophylaxis group) and included 2 patients with fatal events (one with hematoma and thromboses, one with gastrointestinal bleeding). Two patients experienced hypersensitivity reactions and recovered after concizumab discontinuation.

Marstacimab (Hympavzi)

Marstacimab (Hympavzi), a tissue factor pathway inhibitor (TFPI) antagonist, was approved by the U.S. Food and Drug Administration (FDA) in 2024 to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ≥12 years of age with hemophilia A (congenital factor VIII [FVIII] deficiency) without FVIII inhibitors or hemophilia B (congenital factor IX [FIX] deficiency) without FIX inhibitors. Marstacimab is the first TFPI approved for the treatment of hemophilia A and B. Unlike traditional hemophilia treatments that replace clotting factors, concizumab reduces the amount and activity of naturally occurring TFPI. This increases the amount of thrombin that is generated resulting in the

prevention of or a reduction in bleeding episodes. Marstacimab is administered as a once-weekly subcutaneous injection

The safety and efficacy of marstacimab to prevent or reduce the frequency of bleeding episodes was evaluated adult and pediatric patients (N=116; aged 12 years and older and 35 kg or greater) with severe hemophilia A without FVIII inhibitors or severe hemophilia B without FIX inhibitors enrolled in the open-label two- phase BASIS study (NCT03938792). Patients completed a 6-month observational phase where they continued factor-based therapy; patients were separated into 2 groups based on what they received prior to study entry (on demand (n=33) or routine prophylaxis (n=83)). Following the observational phase, patients were entered into the 12-month marstacimab prophylaxis phase.

Marstacimab prophylaxis demonstrated superiority over on-demand factor-based therapy in incidences of treated bleeds, spontaneous bleeds, joint bleeds, total bleeds and target joint bleeds according to the following table:

Annualized Bleeding Rate with Marstacimab-hncq Prophylaxis Versus On-Demand Factor-Based Therapy in Patients 12 Years or 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)	Marstacimab-hncq Prophylaxis During 12-Month ATP (N=33)
Treated bleeds (primary outcome)		
ABR (95% CI)	38 (31.03 to 46.54)	3.18 (2.09 to 4.85)
Ratio vs OD (95% CI)	*0.084 (0.059 to 0.119)*	
Spontaneous bleeds, treated		
ABR (95% CI)	30.93 (24.12 to 39.67)	2.44 (1.61 to 3.69)
Ratio vs OD (95% CI)	*0.079 (0.054 to 0.114)*	
Joint bleeds, treated		
ABR (95% CI)	32.86 (26.15 to 41.29)	2.83 (1.81 to 4.44)
Ratio vs OD (95% CI)	*0.086 (0.059 to 0.125)*	
Total bleeds, treated and untreated		
ABR (95% CI)	47.76 (39.6 to 57.6)	7.39 (5.08 to 10.74)
Ratio vs OD (95% CI)	*0.155 (0.116 to 0.207)*	

Target joint bleeds, treated		
ABR (95% CI)	23.18 (17.2 to 13.24)	1.84 (1.06 to 3.17)
Ratio vs OD (95% CI)	*0.079 (0.051 to 0.124)*	
ABR = Annualized Bleeding Rate; CI = Confidence Interval; OD = On-Demand; OP = Observational Phase; ATP = Active Treatment Phase		

Marstacimab-hncq 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 according to the following table:

Annualized Bleeding Rate with Marstacimab-hncq Prophylaxis vs Previous Routine Factor-Based Prophylaxis in Patients 12 Years or 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)	Marstacimab-hncq Prophylaxis During 12-Month ATP (N=83)
Treated bleeds (primary outcome)		
ABR (95% CI)	7.85 (5.09 to 10.61)	5.08 (3.4 to 6.77)
Difference vs RP (95% CI)	*-2.77 (-5.37 to -0.16)*	
Spontaneous bleeds, treated		
ABR (95% CI)	5.86 (3.54 to 8.19)	3.78 (2.25 to 5.31)
Difference vs RP (95% CI)	*-2.09 (-4.23 to 0.06)*	
Joint bleeds, treated		
ABR (95% CI)	5.66 (3.33 to 7.98)	4.13 (2.59 to 5.67)
Difference vs RP (95% CI)	*-1.53 (-3.7 to 0.64)*	
Total bleeds, treated and untreated		
ABR (95% CI)	8.84 (5.97 to 11.72)	5.97 (4.13 to 7.81)
Difference vs RP (95% CI)	*-2.87 (-5.61 to -0.12)*	

Target joint bleeds, treated		
ABR (95% CI)	3.36 (1.59 to 5.14)	2.51 (1.25 to 3.76)
Difference vs RP (95% CI)	*-0.86 (-2.41 to 0.7)*	
ABR = Annualized Bleeding Rate; CI = Confidence Interval; OP = Observational Phase; ATP = Active Treatment Phase; RP = Routine Prophylaxis		

Adverse reactions occurring in 3% or greater of patients treated with marstacimab included injection site reaction, headache, and pruritus.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation and continuation of subcutaneous non-clotting factor prophylactic therapy for hemophilia **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member has been seen by a board-certified hematologist-oncologist or hematologist in the past 12 months – documentation from the medical record must be provided, including **ALL** of the following:
    a. Complete hematologic and musculoskeletal assessment performed by the physician
    b. Factor replacement protocol (including dosing for acute and prophylactic management) developed or evaluated by a board-certified hematologist or hematologist-oncologist (or a physician extender practicing under their supervision) in the past 12 months
2. Requested product is prescribed by a board-certified hematologist or hematologist-oncologist (or a physician extender practicing under the supervision of a hematologist or hematologist-oncologist)
3. Member maintains a treatment log documenting any bleeds and required treatment for 12 consecutive months
    a. Hemlibra requests – a copy of the treatment log with at least 12 months of tracking bleeds must be submitted (6 months of data will be allowed if initiating therapy)
4. Concizumab (Alhemo), emicizumab-kxwh (Hemlibra), fitusiran (Qfitlia), and marstacimab (Hympavzi) will not be used in combination
5. Member meets product specific criteria outlined in Table 1.

Table 1: Criteria for use of subcutaneous non-clotting factor prophylactic therapy for hemophilia

Product	Required Criteria (ALL must be met)
Concizumab *Alhemo*	Initiation of therapy: 1. Member is diagnosed with either of the following: a. Hemophilia A and **ALL** of the following are met: i. Member has high-titer inhibitors to factor VIII (≥ 5 Bethesda units [BU]) **AND** use will not be in combination with immune tolerance therapy (ITT) – recent (within the past 90 days) laboratory documentation must be provided ii. Member meets **ONE** of the following: (1) Member's endogenous (baseline, not treated) factor VIII is less than or equal to 1 IU/dL (1%) **AND** member is transitioning from a prophylactic factor replacement regimen – recent (within the past 90 days) laboratory documentation must be provided (2) Member's endogenous (baseline, not treated) factor VIII is greater than 1 IU/dL (1%) but less than or equal to 5 IU/dL (5%) **AND** the provider has determined that the patient has a bleed history that simulates severe hemophilia A **AND** member is transitioning from a prophylactic factor replacement regimen – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided (3) Member's endogenous (baseline, not treated) factor VIII is greater than 5 IU/dL (5%) and less than or equal to 40 IU/dL (40%) **AND** member has documented history of 2 or more bleeds into large joints (i.e., ankles, knees, hips, elbows, shoulders) **AND** the member has had clinically evident bleeding (defined as: 1 or more episodes of spontaneous bleeding into a joint or into the central nervous system; or 4 or more episodes of soft tissue bleeding in an 8 week period) during a two month trial of at least one of the following factor VIII products when used as part of a factor replacement protocol for prophylactic management of bleeding – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided: (a) Human (plasma-derived) Factor VIII: Hemofil M, Monoclate-P (b) Recombinant Factor VIII: Advate, Adynovate, Afstyla, Eloctate, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, ReFacto, Xyntha b. Hemophilia B and **ALL** of the following are met:

	i. Member has high-titer inhibitors to factor IX (≥ 5 Bethesda units [BU]) **AND** use will not be in combination with immune tolerance therapy (ITT) – recent (within the past 90 days) laboratory documentation must be provided ii. Member meets **ONE** of the following: (1) Member's endogenous (baseline, not treated) factor IX is less than or equal to 2 IU/dL (2%) **AND** member is transitioning from a prophylactic factor replacement regimen – recent (within the past 90 days) laboratory documentation must be provided (2) Member's endogenous (baseline, not treated) factor IX is greater than 2 IU/dL (2%) but less than or equal to 5 IU/dL (5%) **AND** the provider has determined that the patient has a bleed history that simulates severe hemophilia B **AND** member is transitioning from a prophylactic factor replacement regimen – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided (3) Member's endogenous (baseline, not treated) factor IX is greater than 5 IU/dL (5%) and less than or equal to 40 IU/dL (40%) **AND** member has documented history of 2 or more bleeds into large joints (i.e., ankles, knees, hips, elbows, shoulders) **AND** the member has had clinically evident bleeding (defined as: 1 or more episodes of spontaneous bleeding into a joint or into the central nervous system; or 4 or more episodes of soft tissue bleeding in an 8 week period) during a two month trial of at least one of the following factor IX products when used as part of a factor replacement protocol for prophylactic management of bleeding – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided: (a) Human (plasma-derived) Factor IX: AlphaNine SD, Mononine (b) Recombinant Factor IX: BeneFIX, Ixinity, RIXUBIS 2. Member was previously approved by Florida Blue for a prophylaxis regimen Note: Provider agrees to discontinue prophylaxis regimen. Any prior authorization for a prophylaxis regimen will be discontinued. 3. Dose does not exceed the following: a. Loading dose: 1 mg/kg x 1 dose b. Initial maintenance dose: 0.2 mg/kg daily x 4 weeks c. Maintenance dose will be titrated to maintain a concizumab plasma concentration above 200 ng/mL **Approval duration**: 6 months <u>Continuation of therapy</u>:

	1. Member was previously approved by Florida Blue OR the member has previously met all initiation criteria 2. Member demonstrates a beneficial response to treatment as evidenced by a reduction in the number of bleeding events or stabilization of disease – documentation from the treatment log and/or medical record must be provided 3. Member has achieved and maintains a concizumab plasma concentration above 200 ng/mL as evidenced by two separate assessments while treated at a stable dose – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided 4. Dose does not exceed the 0.2 mg/kg daily with the following exception: a. Member requires a dose higher than 0.2 mg/kg daily to achieve and maintain a concizumab plasma concentration above 200 ng/mL – recent (within the past 90 days) laboratory documentation must be provided **Approval duration**: 1 year
Emicizumab-kxwh *Hemlibra*	<u>Initiation of therapy</u>: 1. Member is diagnosed with hemophilia A 2. Member meets **ONE** of the following: a. Member has high-titer inhibitors to factor VIII (≥ 5 Bethesda units [BU]) **AND** use will not be in combination with immune tolerance therapy (ITT) – recent (within the past 90 days) laboratory documentation must be provided b. Member's endogenous (baseline, not treated) factor VIII is less than or equal to 1 IU/dL (1%) **AND** member is transitioning from a prophylactic factor replacement regimen – recent (within the past 90 days) laboratory documentation must be provided c. Member's endogenous (baseline, not treated) factor VIII is greater than 1 IU/dL (1%) but less than or equal to 5 IU/dL (5%) **AND** the provider has determined that the patient has a bleed history that simulates severe hemophilia A **AND** member is transitioning from a prophylactic factor replacement regimen – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided d. Member's endogenous (baseline, not treated) factor VIII is greater than 5 IU/dL (5%) and less than or equal to 40 IU/dL (40%) **AND** member has documented history of 2 or more bleeds into large joints (i.e., ankles, knees, hips, elbows, shoulders) **AND** the member has had clinically evident bleeding (defined as: 1 or more episodes of spontaneous bleeding into a joint or into the central nervous system; or 4 or more episodes of soft tissue bleeding in an 8 week period) during a two month trial of at least one of the following factor VIII products when used as part of a factor replacement protocol for prophylactic management of bleeding – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided:

	i. Human (plasma-derived) Factor VIII: Hemofil M, Monoclate-P ii. Recombinant Factor VIII: Advate, Adynovate, Afstyla, Eloctate, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, ReFacto, Xyntha e. Member was previously approved for Hemlibra by another health plan – documentation of a recent (within 90 days prior to authorization request) health plan-paid claim for Hemlibra must be provided 3. Dose does not exceed: a. Initial dose: 3 mg/kg once weekly for 4 weeks b. Maintenance dose: 1.5 mg/kg once weekly 4. Maximum dispensed quantity does not exceed: a. <u>Initial weight-based limits – applicable to first 28 days of therapy ONLY</u>: • 15 kg or less: four 30 mg/1 mL vials (max 4 mL) • > 15 kg and ≤ 20 kg: four 60 mg/0.4 mL vials (max 1.6 mL) • > 20 kg and ≤ 35 kg: four 105 mg/0.7 mL vials (max 2.8 mL) • > 35 kg and ≤ 50 kg: four 150 mg/mL vials (max 4 mL) • > 50 kg and ≤ 60 kg: twelve 60 mg/0.4 mL vials (max 4.8 mL) • > 60 kg and ≤ 70 kg: eight 105 mg/0.7 mL vials (max 5.6 mL) • > 70 kg and ≤ 80 kg: sixteen 60 mg/0.4 mL (max 6.4 mL) • > 80 kg and ≤ 100 kg: eight 150 mg/mL vials (max 8 mL) • > 100 kg and ≤ 105 kg: twelve 105 mg/0.7 mL vials (max 8.4 mL) • > 105 kg and ≤ 120 kg: twenty-four 60 mg/0.4 mL vials (max 9.6 mL) • > 120 kg and ≤ 140 kg: sixteen 105/0.7 mL vials (max 11.2 mL) • > 140 kg and ≤ 150 kg: twelve 150 mg/mL vials (max 12 mL) • > 150 kg and ≤ 160 kg: thirty-two 60 mg/0.4 mL vials (max 12.8 mL) • > 160 kg and ≤ 175 kg: twenty 105 mg/0.7 mL vials (max 14 mL) • > 175 kg and ≤ 180 kg: thirty-six 60 mg/0.4 mL vials (max 14.4 mL) • > 180 kg and ≤ 200 kg: sixteen 150 mg/mL vials (max 16 mL) b. <u>Maintenance weight-based limits per 28 days</u>: • 20 kg or less: four 30 mg/1 mL vials (max 4 mL) • > 20 kg and ≤ 40 kg: four 60 mg/0.4 mL vials (max 1.6 mL) • > 40 kg and ≤ 70 kg: four 105 mg/0.7 mL vials (max 2.8 mL) • > 70 kg and ≤ 80 kg: eight 60 mg/0.4 mL vials (max 3.2 mL)

	• > 80 kg and ≤ 100 kg: four 150 mg/1 mL vials (max 4 mL) • > 100 kg and ≤ 120 kg: twelve 60 mg/0.4 mL (max 4.8 mL) **OR** four 60 mg/0.4 mL vials (max 1.6 mL) **plus** four 105 mg/0.7 mL vials (max 2.8 mL) • > 120 kg and ≤ 140 kg: eight 105 mg/0.7 mL vials (max 5.6 mL) • > 140 kg and ≤ 160 kg: sixteen 60 mg/0.4 mL vials (max 6.4 mL) • > 160 kg and ≤ 200 kg: eight 150 mg/1 mL vials (max 8 mL) **Approval duration**: 6 months <u>Continuation of therapy</u>: 1. Member was previously approved by Florida Blue OR the member has previously met all initiation criteria 2. Member is diagnosed with hemophilia A 3. Member demonstrates a beneficial response to treatment with Hemlibra as evidenced by a reduction in number of bleeding events or stabilization of disease – documentation from the treatment log and/or medical record must be provided 5. Dose does not exceed: 1.5 mg/kg once weekly 6. Maximum dispensed quantity does not exceed: a. <u>Maintenance weight-based limits per 28 days</u>: • 20 kg or less: four 30 mg/1 mL vials (max 4 mL) • > 20 kg and ≤ 40 kg: four 60 mg/0.4 mL vials (max 1.6 mL) • > 40 kg and ≤ 70 kg: four 105 mg/0.7 mL vials (max 2.8 mL) • > 70 kg and ≤ 80 kg: eight 60 mg/0.4 mL vials (max 3.2 mL) • > 80 kg and ≤ 100 kg: four 150 mg/1 mL vials (max 4 mL) • > 100 kg and ≤ 120 kg: twelve 60 mg/0.4 mL (max 4.8 mL) **OR** four 60 mg/0.4 mL vials (max 1.6 mL) **plus** four 105 mg/0.7 mL vials (max 2.8 mL) • > 120 kg and ≤ 140 kg: eight 105 mg/0.7 mL vials (max 5.6 mL) • > 140 kg and ≤ 160 kg: sixteen 60 mg/0.4 mL vials (max 6.4 mL) • > 160 kg and ≤ 200 kg: eight 150 mg/1 mL vials (max 8 mL) **Approval duration**: 1 year
Fitusiran Qfitlia	<u>Initiation of therapy:</u> 1. Member is diagnosed with either of the following: a. Hemophilia A and **ONE** of the following is met: i. Member's endogenous (baseline, not treated) factor VIII is less than or equal to 1 IU/dL (1%) **AND** member is transitioning from a prophylactic factor replacement regimen – recent (within the past 90 days) laboratory documentation must be provided

	ii. Member's endogenous (baseline, not treated) factor VIII is greater than 1 IU/dL (1%) but less than or equal to 5 IU/dL (5%) **AND** the provider has determined that the patient has a bleed history that simulates severe hemophilia A **AND** member is transitioning from a prophylactic factor replacement regimen – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided iii. Member's endogenous (baseline, not treated) factor VIII is greater than 5 IU/dL (5%) and less than or equal to 40 IU/dL (40%) **AND** member has documented history of 2 or more bleeds into large joints (i.e., ankles, knees, hips, elbows, shoulders) **AND** the member has had clinically evident bleeding (defined as: 1 or more episodes of spontaneous bleeding into a joint or into the central nervous system; or 4 or more episodes of soft tissue bleeding in an 8 week period) during a two month trial of at least one of the following factor VIII products when used as part of a factor replacement protocol for prophylactic management of bleeding – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided: (1) Human (plasma-derived) Factor VIII: Hemofil M, Monoclate-P (2) Recombinant Factor VIII: Advate, Adynovate, Afstyla, Eloctate, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, ReFacto, Xyntha b. Hemophilia B and **ONE** of the following is met: i. Member's endogenous (baseline, not treated) factor IX is less than or equal to 2 IU/dL (2%) **AND** member is transitioning from a prophylactic factor replacement regimen – recent (within the past 90 days) laboratory documentation must be provided ii. Member's endogenous (baseline, not treated) factor IX is greater than 2 IU/dL (2%) but less than or equal to 5 IU/dL (5%) **AND** the provider has determined that the patient has a bleed history that simulates severe hemophilia B **AND** member is transitioning from a prophylactic factor replacement regimen – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided iii. Member's endogenous (baseline, not treated) factor IX is greater than 5 IU/dL (5%) and less than or equal to 40 IU/dL (40%) **AND** member has documented history of 2 or more bleeds into large joints (i.e., ankles, knees, hips, elbows, shoulders) **AND** the member has had clinically evident bleeding (defined as: 1 or more episodes of spontaneous bleeding into a joint or into the central nervous system; or 4 or more episodes of soft tissue bleeding in an 8 week period) during a two month trial of at least one of the following factor IX products when used as part of a factor replacement protocol for prophylactic management of bleeding – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided: (1) Human (plasma-derived) Factor IX: AlphaNine SD, Mononine (2) Recombinant Factor IX: BeneFIX, Ixinity, RIXUBIS 2. Member was previously approved by Florida Blue for a prophylaxis regimen

	Note: Provider agrees to discontinue prophylaxis regimen. Any prior authorization for a prophylaxis regimen will be discontinued. 3. Dose does not exceed 50 mg every 2 months **Approval duration**: 6 months Continuation of therapy: 1. Member was previously approved by Florida Blue OR the member has previously met all initiation criteria 2. Member demonstrates a beneficial response to treatment as evidenced by a reduction in the number of bleeding events or stabilization of disease – documentation from the treatment log and/or medical record must be provided 3. Dose does not exceed 50 mg every month **Approval duration**: 1 year
Marstacimab *Hympavzi*	<u>Initiation of therapy</u>: 4. Member is diagnosed with either of the following: a. Hemophilia A and **ONE** of the following is met: i. Member's endogenous (baseline, not treated) factor VIII is less than or equal to 1 IU/dL (1%) **AND** member is transitioning from a prophylactic factor replacement regimen – recent (within the past 90 days) laboratory documentation must be provided ii. Member's endogenous (baseline, not treated) factor VIII is greater than 1 IU/dL (1%) but less than or equal to 5 IU/dL (5%) **AND** the provider has determined that the patient has a bleed history that simulates severe hemophilia A **AND** member is transitioning from a prophylactic factor replacement regimen – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided iii. Member's endogenous (baseline, not treated) factor VIII is greater than 5 IU/dL (5%) and less than or equal to 40 IU/dL (40%) **AND** member has documented history of 2 or more bleeds into large joints (i.e., ankles, knees, hips, elbows, shoulders) **AND** the member has had clinically evident bleeding (defined as: 1 or more episodes of spontaneous bleeding into a joint or into the central nervous system; or 4 or more episodes of soft tissue bleeding in an 8 week period) during a two month trial of at least one of the following factor VIII products when used as part of a factor replacement protocol for prophylactic management of bleeding – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided: (1) Human (plasma-derived) Factor VIII: Hemofil M, Monoclate-P

	(2) Recombinant Factor VIII: Advate, Adynovate, Afstyla, Eloctate, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, ReFacto, Xyntha b. Hemophilia B and **ONE** of the following is met: i. Member's endogenous (baseline, not treated) factor IX is less than or equal to 2 IU/dL (2%) **AND** member is transitioning from a prophylactic factor replacement regimen – recent (within the past 90 days) laboratory documentation must be provided ii. Member's endogenous (baseline, not treated) factor IX is greater than 2 IU/dL (2%) but less than or equal to 5 IU/dL (5%) **AND** the provider has determined that the patient has a bleed history that simulates severe hemophilia B **AND** member is transitioning from a prophylactic factor replacement regimen – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided iii. Member's endogenous (baseline, not treated) factor IX is greater than 5 IU/dL (5%) and less than or equal to 40 IU/dL (40%) **AND** member has documented history of 2 or more bleeds into large joints (i.e., ankles, knees, hips, elbows, shoulders) **AND** the member has had clinically evident bleeding (defined as: 1 or more episodes of spontaneous bleeding into a joint or into the central nervous system; or 4 or more episodes of soft tissue bleeding in an 8 week period) during a two month trial of at least one of the following factor IX products when used as part of a factor replacement protocol for prophylactic management of bleeding – documentation from the medical record and recent (within the past 90 days) laboratory documentation must be provided: (1) Human (plasma-derived) Factor IX: AlphaNine SD, Mononine (2) Recombinant Factor IX: BeneFIX, Ixinity, RIXUBIS 5. Member does not have inhibitors to factor VIII or IX 6. Member was previously approved by Florida Blue for a prophylaxis regimen Note: Provider agrees to discontinue prophylaxis regimen. Any prior authorization for a prophylaxis regimen will be discontinued. 7. Dose does not exceed the following: a. Loading dose: 300 mg (two 150 mg injections) one time b. Maintenance dose: 150 mg once a week starting one week after the maintenance dose **Approval duration**: 6 months <u>Continuation of therapy</u>:

	4. Member was previously approved by Florida Blue OR the member has previously met all initiation criteria 5. Member demonstrates a beneficial response to treatment as evidenced by a reduction in the number of bleeding events or stabilization of disease – documentation from the treatment log and/or medical record must be provided 6. Dose does not exceed 150 mg once a week with the following exception: a. If member continues to experience spontaneous breakthrough bleeding episode (as evidenced by documentation from the treatment log), dose may be increased to 300 mg weekly – documentation from the treatment log must be provided **Approval duration**: 1 year

DOSAGE/ADMINISTRATION:

Concizumab (Alhemo)

- Injection:
  - 60 mg/1.5 mL (40 mg/mL) in a single-patient-use prefilled pen
  - 150 mg/1.5 mL (100 mg/mL) in a single-patient-use prefilled pen
  - 300 mg/3 mL (100 mg/mL) in a single-patient-use prefilled pen
- Concizumab should be administered once-daily
- Recommended dosing regimen:
  - Day 1: Loading dose of 1 mg/kg
  - Day 2: Once-daily dose of 0.2 mg/kg until individualization of maintenance dose
  - 4 weeks after initiation of treatment: For dose optimization measure concizumab-mtci plasma concentration by Concizumab Enzyme-Linked Immunosorbent Assay (ELISA) prior to administration of next scheduled dose. An FDA-authorized test for the measurement of concizumab-mtci concentration in plasma is not currently available.
  - Once the concizumab-mtci concentration result is available, individualize the maintenance dose of concizumab no later than 8 weeks after initiation of treatment, based on the following concizumab-mtci- plasma concentrations:
    - Less than 200 ng/mL: adjust to a once-daily dose of 0.25 mg/kg
    - 200 to 4,000 ng/mL: continue once-daily dose of 0.2 mg/kg
    - Greater than 4,000 ng/mL: adjust to a once-daily dose of 0.15 mg/kg
- The calculated dose is rounded off to the nearest injectable dose as follows:
  - 60 mg/1.5 mL (40 mg/mL) in increments of 0.4 mg (brown label)
  - 150 mg/1.5 mL (100 mg/mL) in increments of 1 mg (gold label)
  - 300 mg/3 mL (100 mg/mL) in increments of 1 mg (white label)

- Additional measurements of concizumab-mtci plasma concentration should be taken at routine clinical follow-ups provided the patient has been on the same maintenance dose for 8 weeks of treatment to ensure steady-state plasma concentration. Maintenance of concizumab plasma concentration above 200 ng/mL is important to decrease the risk of bleeding episodes. If concizumab-mtci plasma concentration remains below 200 ng/mL at two consecutive measurements, the benefits of continued Alhemo® treatment should be evaluated versus the potential risk of bleeding events, and alternative therapies if available should be considered. As Alhemo® is dosed by body weight (mg/kg), it is important to recalculate the dose when patients experience body weight changes.
- Missed Dose
    - Adherence to daily dosing of Alhemo® is important to maintain protection against bleeding. This is especially important during the initial 4 weeks of treatment to ensure a correct maintenance dose is established. Patients who miss a dose during the initial 4-week period should inform their healthcare professional and resume once-daily dosing at the initial 0.2 mg/kg dose level.
- Missed Doses Once the Maintenance Dose Has Been Established
    - The following dosing guidelines should apply ONLY when a patient has forgotten to or neglected to take their once-daily maintenance dose:
        - 1 missed dose: Resume once-daily treatment at the maintenance dose level
        - 2 to 6 missed doses: Resume treatment with a double dose followed by once-daily treatment at the maintenance dose level
        - 7 or more missed doses: Physician should be contacted, and a new loading dose should be considered
- Management of Breakthrough Bleeds
    - No dose adjustment is required in the case of breakthrough bleeds.

Emicizumab-kxwh (Hemlibra)

- Injection:
    - 12 mg/0.4 mL
    - 30 mg/mL
    - 60 mg/0.4 mL
    - 105 mg/0.7 mL
    - 150 mg/mL
    - 300 mg/2 mL (150 mg/mL)
- 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly

Fitusiran (Qfitlia)

- Injection:
    - 50 mg/0.5 mL (100 mg/mL) in a single-dose prefilled pen

    - 20 mg/0.2 mL (100 mg/mL) in a single-dose vial
- Starting dose: 50 mg once every 2 months (2.1).
- Monitor AT activity using an FDA-cleared test.
- Maintain AT activity between 15–35% by adjusting the dose and/or frequency of administration

Marstacimab (Hympavzi)

- Injection:
    - 150 mg/mL in a single-dose prefilled syringe
- Loading dose: 300 mg (two 150 mg injections) by subcutaneous injection
- 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

PRECAUTIONS:

Concizumab (Alhemo)

- Thromboembolic Events: Inform patients of the signs and symptoms of thromboembolic events. Monitor patients for thromboembolic events. Advise patients to report these signs and symptoms, and if they occur discontinue prophylaxis.
- Hypersensitivity Reactions: In the event of a severe hypersensitivity reaction, discontinue treatment.
- Increased Laboratory Values of Fibrin D dimer and Prothrombin Fragment 1+2: Concizumab increases values of fibrin D dimer and prothrombin fragment 1+2.

Emicizumab-kxwh (Hemlibra)

- Cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate was administered for 24 hours or more to patients receiving Hemlibra prophylaxis. Monitor for the development of thrombotic microangiopathy and thrombotic events if aPCC is administered. Discontinue aPCC and suspend dosing if symptoms occur.

Fitusiran (Qfitlia)

- Hepatotoxicity: Obtain liver tests at baseline and then monthly for at least 6 months after initiating QFITLIA and after dose increases, and periodically thereafter. Liver test elevations may require QFITLIA interruption or discontinuation

Marstacimab (Hympavzi)

- Thromboembolic Events: Thromboembolic events may occur. Interrupt prophylaxis if symptoms occur.

- Hypersensitivity: Hypersensitivity reactions may occur. In the event of a severe allergic reaction, discontinue treatment.
- Embryofetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception.

BILLING/CODING INFORMATION:

HCPCS Coding

J7170	Injection, emicizumab-kxwh, 0.5 mg
J7172	Injection, marstacimab-hncq, 0.5 mg
J3590	Unclassified biologics (Alhemo and Qfitlia ONLY)

ICD-10 Diagnosis Codes That Support Medical Necessity

D66	Hereditary factor VIII deficiency
D67	Hereditary factor IX deficiency

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

Clotting Factors and Coagulant Drug Products, 09-J0000-34

Etranacogene Dezaparvovec (Hemgenix), 09-J4000-44

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 05/14/25.

GUIDELINE UPDATE INFORMATION:

04/01/25	New Medical Coverage Guideline.
07/01/25	Revised position statement. Added HCPCS code J7172.