BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

ALHEMO® (concizumab-mtci) subcutaneous injection
HEMLIBRA® (emicizumab-kxwh) subcutaneous injection
HYMPAVZI™ (marstacimab-hncq) subcutaneous injection
QFITLIA™ (fitusiran) subcutaneous injection
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

ALHEMO (concizumab-mtci) subcutaneous injection

- **Criteria for initial therapy:** Alhemo (concizumab-mtci) subcutaneous injection and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Hematologist

  2. Individual is 12 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Severe hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors
    b. Severe hemophilia B (congenital factor IX deficiency) with factor IX inhibitors
4. Request is for routine prophylaxis to prevent or reduce the frequency of bleeding episodes
5. Individual has severe hemophilia defined as factor activity less than 1%
6. There is documentation of a negative pregnancy test in a woman of childbearing potential
7. Individual will not use Alhemo concurrently with ongoing Immune Tolerance Induction (ITI), a desensitization strategy
8. Individual does not have **ANY** of the following:
    a. History of thromboembolic disease (e.g., arterial and venous thrombosis, myocardial infarction, pulmonary embolism, cerebral infarction/thrombosis, deep vein thrombosis, and peripheral artery occlusion)
    b. Current clinical signs of, or treatment for thromboembolic disease
9. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Alhemo (concizumab-mtci) subcutaneous injection and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Hematologist
2. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors
    b. Hemophilia B (congenital factor IX deficiency) with factor IX inhibitors
3. Individual's condition has responded while on therapy with response defined as a reduction in the following:
    a. Frequency of bleeding episodes
    b. Severity of bleeding episodes

4. Individual has been adherent with the medication

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual is not currently taking drugs which may cause severe adverse reactions or significant drug interactions that may require discontinuation such as concurrent use of activated prothrombin complex concentrate that results in:
    a. Thromboembolic events
    b. Hypersensitivity reaction

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

HEMLIBRA (emicizumab-kxwh)

- **Criteria for initial therapy:** Hemlibra (emicizumab-kxwh) subcutaneous injection and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Hematologist

2. Individual is newborn or older

3. Individual has a confirmed diagnosis of hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors

4. Individual has **ONE** of the following:
    a. Severe hemophilia A (defined as endogenous factor VIII less than 1 International Unit per deciliter [1IU/dL])
    b. Mild to moderate hemophilia A (defined as endogenous factor VIII less than 40 IU/dl [less than 40%], but greater than or equal to 1 IU/dl) and **ONE** of the following:
        i. Has one or more episodes of spontaneous bleeding into joints
        ii. Has one or more episodes of severe, life-threatening, or spontaneous bleeding events
        iii. Has a phenotype hemophilia determined by individual's risk factors that increase the risk of a clinically significant bleed (ex., participation in activities likely to cause injury/trauma,

comorbid conditions affecting functional ability and physical coordination, or history of a clinically significant bleed)

5. Requested agent is for routine prophylaxis to prevent or reduce the frequency of bleeding episodes and **ONE** of the following:
    a. If switching from bypassing agents (i.e., NovoSeven RT, SevenFact, FEIBA), individual will discontinue prophylactic bypassing agents the day before starting Hemlibra prophylaxis
    b. If switching from prophylactic factor VIII agents, they may be continued during the first week of Hemlibra prophylaxis

6. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Hemlibra (emicizumab-kxwh) subcutaneous injection and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Hematologist

2. Individual has a confirmed diagnosis of hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors

3. Individual has **ONE** of the following:
    a. Severe hemophilia A (defined as endogenous factor VIII less than 1 International Unit per deciliter [1IU/dL])
    b. Mild to moderate hemophilia A (defined as endogenous factor VIII less than 40 IU/dl [less than 40%], but greater than or equal to 1 IU/dl) and **ONE** of the following:
        i. Has one or more episodes of spontaneous bleeding into joints
        ii. Has one or more episodes of severe, life-threatening, or spontaneous bleeding events
        iii. Has a phenotype hemophilia determined by individual's risk factors that increase the risk of a clinically significant bleed (e.g., participation in activities likely to cause injury/trauma, comorbid conditions affecting functional ability and physical coordination, or history of a clinically significant bleed)

4. Individual's condition has responded while on therapy with response defined as a reduction in the following:
    a. Frequency of bleeding episodes
    b. Severity of bleeding episodes

5. Individual has been adherent with the medication

6. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Individual is not currently taking drugs which may cause severe adverse reactions or significant drug interactions that may require discontinuation such as concurrent use of activated prothrombin complex concentrate that results in:
    a. Thrombotic Microangiopathy
    b. Thrombocytopenia
    c. Microangiopathic hemolytic anemia
    d. Acute kidney injury
    e. Thromboembolism

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

HYMPAVZI (marstacimab-hncq) subcutaneous injection

- **Criteria for initial therapy:** Hympavzi (marstacimab-hncq) subcutaneous injection and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Hematologist

2. Individual is 12 years of age or older

3. Individual has a confirmed diagnosis of severe hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors or severe hemophilia B (congenital factor IX deficiency) without factor IX inhibitors

4. Request is for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in an individual receiving on-demand or routine prophylactic factor replacement treatment

5. Individual has severe hemophilia defined as factor activity less than 1%

6. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Prior to initiation of Hympavzi, discontinue treatment with clotting factor concentrates (factor VIII or factor IX concentrates), Hympavzi can be started at any time after they have been discontinued

8. Additional doses of Hympavzi to treat breakthrough bleeds will not be used, Factor VIII and factor IX products can be administered for the treatment of breakthrough bleeds in individuals receiving Hympavzi

9. There is documentation of a negative pregnancy test in a woman of childbearing potential

10. Individual does not have a history of previous venous or arterial thromboembolic events, history of coronary artery disease, or ischemic disease

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Hympavzi (marstacimab-hncq) subcutaneous injection and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Hematologist

2. Individual has a confirmed diagnosis of hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors or hemophilia B (congenital factor IX deficiency) without factor IX inhibitors

3. Individual's condition has responded while on therapy with response defined as a reduction in the following:
    a. Frequency of bleeding episodes
    b. Severity of bleeding episodes

4. Requested dose is less than or equal to 300 mg, safety and efficacy of Hympavzi at doses above 300 mg weekly have not been established

5. Individual has been adherent with the medication

6. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Individual is not currently taking drugs which may cause severe adverse reactions or significant drug interactions that may require discontinuation such as concurrent use of activated prothrombin complex concentrate that results in:
    a. Thromboembolic events
    b. Hypersensitivity reaction

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**
2. **Off-Label Use of Cancer Medications**

QFITLIA (fitusiran) subcutaneous injection

- **Criteria for initial therapy:** Qfitlia (fitusiran) subcutaneous injection and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Hematologist
2. Individual is 12 years of age or older
3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Severe hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors
    b. Severe hemophilia B (congenital factor IX deficiency) with or without factor IX inhibitors
4. The request is for routine prophylaxis to prevent or reduce the frequency of bleeding episodes
5. Individual has severe hemophilia defined as factor activity less than 1%
6. If approved, clotting factor concentrates (CFC) or bypassing agent (BPA) prophylaxis will be discontinued no later than 7 days after the initial dose of Qfitlia
7. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Antithrombin (AT) activity is at least 60% or more
    b. Liver function tests including AST, ALT, and total bilirubin
8. Individual does not have **ANY** of the following:

a. History of thrombosis or with established thrombophilia
b. Established hepatic impairment (Child-Pugh Class A, B, and C)

9. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Qfitlia (fitusiran) subcutaneous injection and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Hematologist

2. Individual has a confirmed diagnosis of **ONE** of the following:
   a. Hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors

   b. Hemophilia B (congenital factor IX deficiency) with or without factor IX inhibitors

3. Individual's condition has responded while on therapy with response defined as a reduction in the following:
   a. Frequency of bleeding episodes
   b. Severity of bleeding episodes
   c. Treatment of all bleeding episodes, spontaneous bleeding, joint bleeding
   d. Achieves and maintains antithrombin (AT) activity between 15-35%

4. Individual has been adherent with the medication

5. Requested dose is less than 80 mg monthly

6. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Individual does not have **ANY** of the following:
   a. History of thrombosis or with established thrombophilia
   b. Established hepatic impairment (Child-Pugh Class A, B, and C)

8. Individual is not currently taking drugs which may cause severe adverse reactions or significant drug interactions that may require discontinuation such as concurrent use of activated prothrombin complex concentrate that results in:

a. Thromboembolic events
b. Acute or recurrent gallbladder disease (e.g., cholecystitis, cholelithiasis, pancreatitis)
c. Hepatotoxicity

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Benefit Type:

Pharmacy Benefit:
ALHEMO
HEMLIBRA
HYMPAVZI
QFITLIA
Medical Benefit:
ALHEMO
HEMLIBRA

Coding:

HCPCS: C9399, J3590, J7170

Description:

Alhemo (concizumab-mtci) is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with: hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors and hemophilia B (congenital factor IX deficiency) with FIX inhibitors. Concizumab-mtci is a monoclonal antibody antagonist of endogenous Tissue Factor Pathway Inhibitor (TFPI). Inhibition of TFPI enhances FXa production during the initiation phase of coagulation which leads to improved thrombin generation and clot formation with the goal of achieving hemostasis in patients with Hemophilia A or B with inhibitors. Concizumab-mtci effect is not influenced by the presence of inhibitory antibodies to FVIII or FIX. Concizumab-mtci does not induce or enhance the development of direct inhibitors to FVIII or FIX. The safety and efficacy of concomitant use of Alhemo in patients receiving ongoing Immune Tolerance Induction (ITI), a desensitization strategy for the eradication of inhibitors, have not been established, and no data are available

PHARMACY COVERAGE GUIDELINE

ALHEMO® (concizumab-mtci) subcutaneous injection
HEMLIBRA® (emicizumab-kxwh) subcutaneous injection
HYMPAVZI™ (marstacimab-hncq) subcutaneous injection
QFITLIA™ (fitusiran) subcutaneous injection
Generic Equivalent (if available)

Hemlibra (emicizumab-kxwh) subcutaneous injection is a bispecific factor IXa- and factor X-directed antibody indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors. Hemlibra (emicizumab-kxwh) bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective hemostasis.

Hympavzi (marstacimab-hncq) subcutaneous injection is a tissue factor pathway inhibitor (TFPI) antagonist, a human monoclonal immunoglobulin G type 1 (IgG1) antibody, indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or hemophilia B (congenital factor IX deficiency) without factor IX inhibitors. 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. Marstacimab-hncq neutralizes TFPI activity and enhances coagulation.

Qfitlia (fitusiran) is an antithrombin-directed small interfering ribonucleic acid (siRNA) indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients aged 12 years and older with hemophilia A or B with or without factor VIII or IX inhibitors. Qfitlia (fitusiran) is a double-stranded siRNA that causes degradation of antithrombin (AT) messenger RNA (mRNA) through RNA interference, reducing plasma AT levels. In clinical studies with Qfitlia in hemophilia patients, the primary pharmacodynamic (PD) measure was plasma AT activity. Lower AT activity levels were associated with lower annualized bleeding rates (ABR); however, persistent AT activity <15% is a risk factor for thrombotic events. Qfitlia dosing strategy is based on maintaining plasma AT activity levels between 15–35% with 10, 20, or 50 mg dosing every month or every two months.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Resources:

Alhemo (concizumab-mtci) subcutaneous injection product information, Novo Nordisk, Inc. 12-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 05, 2025.

Hemlibra (emicizumab-kxwh) subcutaneous injection product information, Genentech, Inc. 01-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed August 26, 2024.

Qfitlia (fitusiran) subcutaneous injection product information, Genzyme Corporation. 03-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 05, 2025.

Malec L. Hemophilia A and B: Routine management including prophylaxis. In: UpToDate, Shapiro AD, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2024. Topic last updated October 01, 2024. Accessed October 17, 2024.

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Lewandowska M. Gene therapy and investigational approaches for hemophilia. In: UpToDate, Shapiro AD, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2024. Topic last updated October 01, 2024. Accessed October 11, 2024.

Rind DM, Walton SM, Agboola F, et al.: Valoctocogene roxaparvovec and emicizumab for Hemophilia A: Effectiveness and Value; Final Report. Institute for Clinical and Economic Review, November 20, 2020. https://icerreview.org/material/hemophilia-a-update-final-evidence-report/. Accessed August 28, 2024.

Mahlangu J, Lamas JL, Morales JC, et al. Long-term safety and efficacy of the anti-tissue factor pathway inhibitor marstacimab in participants with severe hemophilia: Phase II study results. Br J Haematol. 2023;200(2):240–248. Accessed October 17, 2024.

Matsushita T, Shapiro A, Abraham A, et al.: Phase 3 Trial of Concizumab in Hemophilia with Inhibitors. NEJM 2023 Aug 30; 389 (9):783-794. Accessed February 06, 2025.

Kenet G, Nolan B, Zulfikar B, et al.: Fitusiran prophylaxis in people with hemophilia A or B who switch from prior BPA/CFC prophylaxis: The ATLAS-PPX trial. Blood 2024 May 30; 143 (22): 2256-2269. Accessed April 23, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03417102: ATLAS-INH: A Phase 3 Study to Evaluate the Efficacy and Safety of Fitusiran in Patients With Hemophilia A or B, With Inhibitory Antibodies to Factor VIII or IX. Available from: http://clinicaltrials.gov. Last update posted March 28, 2022. Last verified March 2022. Accessed April 23, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03417245: ATLAS-A/B: A Phase 3 Study to Evaluate the Efficacy and Safety of Fitusiran in Patients With Hemophilia A or B, Without Inhibitory Antibodies to Factor VIII or IX. Available from: http://clinicaltrials.gov. Last update posted March 28, 2022. Last verified March 2022. Accessed April 23, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03754790: An Open-label, Long-term Safety and Efficacy Study of Fitusiran in Patients With Hemophilia A or B, With or Without Inhibitory Antibodies to Factor VIII or IX. Available from: http://clinicaltrials.gov. Last update posted July 15, 2024. Last verified July 2024. Accessed April 23, 2025.