Clotting Factors, Coagulant Blood Products, & Other Hemostatics

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Ü Instructions for Use

Table of Contents **Page**

Applicable States 1
Coverage Rationale 1
Applicable Codes 9
Background 10
Benefit Considerations 12
Clinical Evidence 12
U.S. Food and Drug Administration 21
References 24
Policy History/Revision Information 26
Instructions for Use 26

Related Policies
None

Applicable States

This Medical Benefit Drug Policy applies to Individual Exchange benefit plans in all states except for Massachusetts, Nevada, and New York.

Coverage Rationale

Ü See Benefit Considerations

Alhemo (concizumab-mtci) has been added to the Review at Launch program. Some members may not be eligible for coverage of this medication at this time. Refer to the Medical Benefit Drug Policy titled Review at Launch for New to Market Medications for additional details.

This policy refers to the following products:

Product	Brand Name
Factor VIIa (recombinant)	NovoSeven® RT [coagulation factor VIIa (recombinant)] Sevenfact® [coagulation factor VIIa (recombinant)-jncw]
Factor XIII (plasma-derived)	Corifact® [factor XIII concentrate (human)]
Factor VIII (plasma-derived)	Hemofil M® [antihemophilic factor (human)]
	Koāte®-DVI [antihemophilic factor (human)]
Factor VIII (plasma-derived) / von Willebrand Factor Complex (plasma-derived)	Alphanate® [antihemophilic factor (human)]
	Humate-P® [antihemophilic factor (human)]
	Wilate® [antihemophilic factor (human)]
Factor VIII (recombinant)	Advate® [antihemophilic factor (recombinant)]
	Kogenate® FS [antihemophilic factor (recombinant)]
	Kovaltry® [antihemophilic factor (recombinant)]
	Novoeight® [antihemophilic factor (recombinant)]
	Nuwiq® [antihemophilic factor (recombinant)]

Product	Brand Name
Factor VIII (recombinant)	Recombinate® [antihemophilic factor (recombinant)]
	Xyntha® [antihemophilic factor (recombinant)]
	Xyntha® Solofuse™ [antihemophilic factor (recombinant)]
Factor IX (plasma-derived)	AlphaNine® SD [coagulation factor IX (human)]
	Profilnine SD® [factor IX complex human)]
Factor IX (recombinant)	BeneFIX® [coagulation factor IX (recombinant)]
	Ixinity® [coagulation factor IX (recombinant)]
	Rixubis® [coagulation factor IX (recombinant)]
Factor IX (recombinant), long-acting	Alprolix® [coagulation factor IX (recombinant), Fc fusion protein]
	Idelvion® [coagulation factor IX (recombinant), albumin fusion protein]
	Rebinyn® [coagulation factor IX (recombinant), GlycoPEGylated]
Anti-Inhibitor Coagulant Complex (plasma-derived)	FEIBA® [anti-inhibitor coagulant complex (human)]
Fibrinogen Concentrate (plasma-derived)	RiaSTAP® [fibrinogen concentrate (human)]
	Fibryga® [fibrinogen (human)]
Factor XIII A-subunit (recombinant)	Tretten® [coagulation factor XIII A-subunit (recombinant)]
Factor VIII (recombinant), long-acting	Adynovate® [antihemophilic factor (recombinant), PEGylated]
	Afstyla® [antihemophilic factor (recombinant)]
	Altuviiio™ [antihemophilic factor (recombinant), Fc-VWF-XTEN, fusion protein-ehtl]
	Eloctate® [antihemophilic factor (recombinant), Fc fusion protein]
	Esperoct® [antihemophilic factor (recombinant), glycopegylated-exei]
	Jivi® [antihemophilic factor (recombinant), PEGylated-aucl]
Factor VIII (recombinant), porcine sequence	Obizur® [antihemophilic factor (recombinant), porcine sequence]
Factor X (plasma-derived)	Coagadex® [coagulation factor X (human)]
Von Willebrand Factor (recombinant)	Vonvendi® [von Willebrand factor (recombinant)]
Bispecific factor IXa- and factor X-directed antibody	Hemlibra® (emicizumab-kxwh)
Tissue factor pathway inhibitor (TFPI) antagonist	Alhemo® (concizumab-mtci)
	Hympavzi™ (marstacimab-hncq)

Congenital Factor XIII Deficiency (i.e., Fibrin Stabilizing Factor Deficiency)

Factor XIII (plasma-derived) [Corifact] is proven and medically necessary when both of the following criteria are met:

- Diagnosis of congenital factor XIII deficiency; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

Coagulation Factor XIII A-subunit (recombinant) [Tretten] is proven and medically necessary when both of the following criteria are met:

- Diagnosis of congenital factor XIII A-subunit deficiency; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**

- Peri-operative management of surgical bleeding; **or**
- Treatment of bleeding episodes

Von Willebrand Disease (VWD)

Factor VIII (plasma-derived)/von Willebrand Factor Complex (plasma-derived) [Humate-P] is proven and medically necessary when both of the following criteria are met:

- **One** of the following:
  - Diagnosis of severe von Willebrand disease; **or**
  - **Both** of the following:
    - Diagnosis of mild or moderate von Willebrand disease; **and**
    - History of failure, contraindication or intolerance to treatment with desmopressin

  and
- **One** of the following:
  - Treatment of bleeding episodes; **or**
  - Peri-operative management of surgical bleeding

Factor VIII (plasma-derived)/von Willebrand Factor Complex (plasma-derived) [Alphanate] is proven and medically necessary when all of the following criteria are met:

- Diagnosis of mild or moderate von Willebrand disease; **and**
- Peri-operative management of surgical bleeding; **and**
- History of failure, contraindication or intolerance to treatment with desmopressin

Factor VIII (plasma-derived)/von Willebrand Factor Complex (plasma-derived) [Wilate] is proven and medically necessary when both of the following criteria are met:

- Diagnosis of von Willebrand disease; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

Von Willebrand factor (recombinant) [Vonvendi] is proven and medically necessary when both of the following criteria are met:

- Diagnosis of von Willebrand disease; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

Congenital Factor VII Deficiency

Factor VIIa (recombinant) [NovoSeven RT] is proven and medically necessary when both of the following criteria are met:

- Diagnosis of congenital factor VII deficiency; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Treatment of bleeding episodes

Hemophilia A (i.e., Factor VIII Deficiency, Classical Hemophilia)

Factor VIII (plasma-derived)/von Willebrand Factor Complex (plasma-derived) [Alphanate or Humate-P], Factor VIII (plasma-derived) [Hemofil M or Koāte-DVI], and Factor VIII (recombinant) [Advate, Kogenate FS, Kovaltry, NovoEight, Nuwiq, or Recombinate] are proven and medically necessary when both of the following criteria are met:

- Diagnosis of hemophilia A; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

Factor VIII (plasma-derived)/von Willebrand Factor Complex (plasma-derived) [Wilate] is proven and medically necessary when both of the following criteria are met:

- Diagnosis of hemophilia A; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Treatment of bleeding episodes

Esperoct [antihemophilic factor (recombinant), glycopegylated-exei] is proven and medically necessary for treatment of hemophilia A for the following:

- Diagnosis of hemophilia A; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

Antihemophilic Factor (recombinant) [Xyntha] is proven and medically necessary for the treatment of hemophilia A when all of the following criteria are met:

- Diagnosis of hemophilia A; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

Antihemophilic Factor (recombinant), FC Fusion Protein [Eloctate] is proven and medically necessary for the treatment of Hemophilia A when all of the following criteria are met:

- Diagnosis of hemophilia A; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

  and
- **One** of the following:
  - **Both** of the following:
    - Dose does not exceed 50 i.u./kg; **and**
    - Infusing no more frequently than every 4 days

    or
  - Requested dosage regimen does not exceed 12.5 i.u./kg/day; **or**
  - **Both** of the following:
    - Patient is less than 6 years of age; **and**
    - **One** of the following:
      - PK testing results suggest that dosing more intensive than 50 i.u./kg is required; **or**
      - PK testing results suggest that dosing more frequently than every 3 to 5 days is required; **or**
      - PK testing results suggest that dosing more intensive that 14.5 i.u./kg/day is required

Antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl [Altuviiio] is proven and medically necessary for the treatment of Hemophilia A when all of the following criteria are met:

- Diagnosis of hemophilia A; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

  and
- **Both** of the following:
  - Dose does not exceed 50 IU/kg; **and**
  - Patient is infusing no more frequently than every 7 days

Antihemophilic Factor (recombinant), Pegylated-aucl [Jivi] is proven and medically necessary for the treatment of Hemophilia A when all of the following criteria are met:

- Diagnosis of hemophilia A; **and**

- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

  and
- Patient has previously received Factor VIII replacement therapy; **and**
- Patient is 12 years of age or older; **and**
- Patient is not to receive routine infusions more than 2 times per week

Antihemophilic Factor (recombinant), Single Chain [Afstyla] is proven and medically necessary for the treatment of Hemophilia A when all of the following criteria are met:
- Diagnosis of hemophilia A; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

  and
- **One** of the following:
  - Patient is not to receive routine infusions more frequently than 3 times per week; **or**
  - **Both** of the following:
    - Patient is less than 12 years of age; **and**
    - Pharmacokinetic (PK) testing results suggest that more frequently than 3 times per week dosing is required

Antihemophilic Factor (recombinant), Pegylated [Adynovate] is proven and medically necessary for the treatment of Hemophilia A when all of the following criteria are met:
- Diagnosis of hemophilia A; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

  and
- **One** of the following:
  - **Both** of the following:
    - Patient is not to receive routine infusions more frequently than 2 times per week; **and**
    - Patient is not to receive a routine dose greater than 50 IU/kg

    or
  - **All** of the following:
    - Patient is less than 12 years of age; **and**
    - Patient is not to receive routine infusions more frequently than 2 times per week; **and**
    - Patient is not to receive a routine dose greater than 70 IU/kg

Concizumab-mtci [Alhemo] is proven and medically necessary for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A with factor VIII inhibitors when all of the following criteria are met:
- For **initial therapy**:
  - Diagnosis of hemophilia A; **and**
  - Patient is 12 years of age or older; **and**
  - Patient has developed high-titer factor VIII inhibitors [≥ 5 Bethesda units (BU)]; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis)
- For **continuation of therapy**:
  - Patient has previously been treated with Alhemo; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**
  - Documentation of positive clinical response to Alhemo therapy

Emicizumab-kxwh [Hemlibra] is proven and medically necessary for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A when all of the following criteria are met:
- For **initial therapy**:
  - **One** of the following:
    - **All** of the following:

- Diagnosis of severe hemophilia A; **and**
- Documentation of endogenous factor VIII level less than 1% of normal factor VIII (< 0.01 i.u./mL); **and**
- Prescriber attestation that the patient is not to receive extended half-life factor VIII replacement products (e.g., Adynovate, Afstyla, Altuviiio, Eloctate, Jivi) for the treatment of breakthrough bleeding episodes

or

- **All** of the following:
  - **One** of the following:
    - **Both** of the following:
      - Diagnosis of moderate hemophilia A; **and**
      - Documentation of endogenous factor VIII level ≥ 1% < 5% (greater than or equal to 0.01 i.u./mL to less than 0.05 i.u./mL)

      or
    - **Both** of the following:
      - Diagnosis of mild hemophilia A; **and**
      - Documentation of endogenous factor VIII level ≥ 5% (greater than or equal to 0.05 i.u./mL)

    and
  - Submission of medical records (e.g., chart notes, laboratory values) documenting a failure to meet clinical goals (e.g., continuation of spontaneous bleeds, inability to achieve appropriate trough level, previous history of inhibitors) after a trial of prophylactic factor VIII replacement products; **and**
  - Prescriber attestation that the patient is not to receive extended half-life factor VIII replacement products (e.g., Adynovate, Afstyla, Altuviiio, Eloctate, Jivi) for the treatment of breakthrough bleeding episodes; **or**
- **Both** of the following:
  - Diagnosis of hemophilia A; **and**
  - Patient has developed high-titer factor VIII inhibitors [≥ 5 Bethesda units (BU)]

and

- Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis)

- For **continuation of therapy**:
  - Patient has previously been treated with Hemlibra; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**
  - Documentation of positive clinical response; **and**
  - Prescriber attestation that the patient is not to receive extended half-life factor VIII replacement products (e.g., Adynovate, Afstyla, Altuviiio, Eloctate, Jivi) for the treatment of breakthrough bleeding episodes

Anti-Inhibitor Coagulant Complex (plasma-derived) [FEIBA] is proven and medically necessary when all of the following criteria are met:

- Diagnosis of hemophilia A; **and**
- Documentation of inhibitors (e.g., Bethesda inhibitor assay); **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

Factor VIIa (recombinant) [NovoSeven RT] is proven and medically necessary when all of the following criteria are met:

- Diagnosis of hemophilia A; **and**
- Documentation of inhibitors (e.g., Bethesda inhibitor assay); **and**
- **One** of the following:
  - Treatment of bleeding episodes; **or**
  - Peri-operative management of surgical bleeding

Factor VIIa (recombinant)-jncw [Sevenfact] is proven and medically necessary when both of the following criteria are met:

- Diagnosis of hemophilia A; **and**
- Treatment and control of bleeding episodes

Factor VIIa (recombinant) [NovoSeven RT] and antihemophilic factor (recombinant), porcine sequence [Obizur] are proven and medically necessary when both of the following criteria are met:

- Diagnosis of acquired factor VIII hemophilia (e.g., acquired hemophilia A, Factor VIII deficiency); **and**
- Treatment or prevention of bleeding episodes

Marstacimab-hncq [Hympavzi] is not medically necessary for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A without factor VIII inhibitors.

Published clinical evidence shows Hympavzi is likely to produce equivalent therapeutic results as other available therapies [e.g., Hemlibra (emicizumab-kxwh)].

Hemophilia B (i.e., Congenital Factor IX Deficiency, Christmas Disease)

Factor IX (plasma-derived) [AlphaNine SD or Profilnine SD] is proven and medically necessary when both of the following criteria are met:

- Diagnosis of hemophilia B; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Treatment of bleeding episodes

Factor IX (recombinant) [BeneFIX or Rixubis], Coagulation Factor IX (recombinant), Fc Fusion Protein (Alprolix) and Coagulation Factor IX (recombinant), albumin fusion protein (Idelvion) are proven and medically necessary when both of the following criteria are met:

- Diagnosis of hemophilia B; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

Coagulation Factor IX (recombinant) [Ixinity] and Coagulation Factor IX (recombinant), GlycoPEGylated) [Rebinyn] are proven and medically necessary for treatment of hemophilia B for the following:

- Diagnosis of hemophilia B; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

Anti-Inhibitor Coagulant Complex (plasma-derived) [FEIBA]and Factor VIIa (recombinant)-jncw [Sevenfact] are proven and medically necessary when all of the following criteria are met:

- Diagnosis of hemophilia B; **and**
- Documentation of inhibitors (e.g., Bethesda inhibitor assay); **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

Factor VIIa (recombinant) [NovoSeven RT] is proven and medically necessary when all of the following criteria are met:

- Diagnosis of hemophilia B; **and**
- Documentation of inhibitors (e.g., Bethesda inhibitor assay); **and**
- **One** of the following:
  - Treatment of bleeding episodes; **or**
  - Peri-operative management of surgical bleeding

Concizumab-mtci [Alhemo] is proven and medically necessary for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia B with factor IX inhibitors when all of the following criteria are met:

- For **initial therapy**:
  - Diagnosis of hemophilia B; **and**
  - Patient is 12 years of age or older; **and**
  - Patient has developed high-titer factor IX inhibitors [≥ 5 Bethesda units (BU)]; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis)
- For **continuation of therapy**:
  - Patient has previously been treated with Alhemo; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**

Documentation of positive clinical response to Alhemo therapy

Marstacimab-hncq [Hympavzi] is proven and medically necessary when all of the following criteria are met

- For **initial therapy**:
  - **One** of the following:
    - **All** of the following:
      - Diagnosis of severe hemophilia B; **and**
      - Documentation of endogenous factor IX level less than 1% of normal factor IX (< 0.01 i.u./mL); **and**
      - Prescriber attestation that the patient is not to receive extended half-life factor IX replacement products (e.g., Alprolix, Idelvion) for the treatment of breakthrough bleeding episodes

      or
    - **All** of the following:
      - **One** of the following:
        - **Both** of the following:
          - Diagnosis of moderate hemophilia B; **and**
          - Documentation of endogenous factor IX level ≥ 1% < 5% (greater than or equal to 0.01 i.u./mL to less than 0.05 i.u./mL)

          or
        - **Both** of the following:
          - Diagnosis of mild hemophilia B; **and**
          - Documentation of endogenous factor IX level ≥ 5% (greater than or equal to 0.05 i.u./mL)

        and
      - Submission of medical records (e.g., chart notes, laboratory values) documenting a failure to meet clinical goals (e.g., continuation of spontaneous bleeds, inability to achieve appropriate trough level, previous history of inhibitors) after a trial of prophylactic factor IX replacement products; **and**
      - Prescriber attestation that the patient is not to receive extended half-life factor IX replacement products (e.g., Alprolix, Idelvion) for the treatment of breakthrough bleeding episodes

    and
  - Patient is 12 years of age or older; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**
  - Patient does not have a history of inhibitors to factor IX
- For **continuation of therapy**:
  - Patient has previously been treated with Hympavzi; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**
  - Documentation of positive clinical response; **and**
  - Prescriber attestation that the patient is not to receive extended half-life factor IX replacement products (e.g., Alprolix, Idelvion) for the treatment of breakthrough bleeding episodes

Fibrinogen Deficiency (i.e., Factor I Deficiency)

Fibrinogen Concentrate (plasma-derived) [Fibryga] is proven and medically necessary when both of the following criteria are met:

- One of the following diagnoses:
  - Acquired fibrinogen deficiency; **or**
  - Congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia

  and
- Treatment of bleeding episodes

Fibrinogen Concentrate (plasma-derived) [RiaSTAP] is proven and medically necessary when both of the following criteria are met:

- Diagnosis of congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia; **and**
- Treatment of bleeding episodes

Glanzmann Thrombasthenia

Factor VIIa (recombinant) [NovoSeven RT] is proven and medically necessary when all of the following criteria are met:

- Diagnosis of Glanzmann's thrombasthenia; **and**
- Refractory to platelet transfusions; **and**
- **One** of the following:
  - Treatment of bleeding episodes; **or**

- Peri-operative management of surgical bleeding

Congenital Factor X Deficiency

Coagulation Factor X (human) [Coagadex] is proven and medically necessary when both of the following criteria are met:

- Diagnosis of congenital Factor X deficiency; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Treatment of bleeding episodes; **or**
  - Peri-operative management of surgical bleeding

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
C9304	Injection, marstacimab-hncq, 0.5 mg
J3490	Unclassified drugs
J3590	Unclassified biologics
J7170	Injection, emicizumab-kxwh, 0.5 mg
J7175	Injection, factor X (human), 1 i.u.
J7177	Injection, human fibrinogen concentrate (Fibryga), 1 mg
J7178	Injection, human fibrinogen concentrate, not otherwise specified, 1 mg
J7179	Injection, von Willebrand factor (recombinant), (Vonvendi), 1 i.u. vWF: RCo
J7180	Injection, factor XIII (antihemophilic factor, human), 1 i.u.
J7181	Injection, factor XIII A-subunit, (recombinant), per i.u. (Tretten)
J7182	Injection, factor VIII, (antihemophilic factor, recombinant), (Novoeight), per i.u.
J7183	Injection, von Willebrand factor complex (human), Wilate, 1 i.u. vWF: RCo
J7185	Injection, factor VIII (antihemophilic factor, recombinant) (XYNTHA), per i.u.
J7186	Injection, antihemophilic factor VIII/von Willebrand factor complex (human), per factor VIII i.u.
J7187	Injection, von Willebrand factor complex (Humate-P), per i.u. VWF: RCO
J7188	Injection, Factor VIII (antihemophilic factor, recombinant) (Obizur), per i.u.
J7189	Factor VIIa (antihemophilic factor, recombinant), (NovoSeven RT), 1 mcg
J7190	Factor VIII (antihemophilic factor, human) per i.u.
J7192	Factor VIII (antihemophilic factor, recombinant) per i.u., not otherwise specified
J7193	Factor IX (antihemophilic factor, purified, nonrecombinant) per i.u.
J7194	Factor IX complex, per i.u.
J7195	Injection, factor IX (antihemophilic factor, recombinant) per i.u., not otherwise specified
J7198	Anti-inhibitor, per i.u.
J7199	Hemophilia clotting factor, not otherwise classified
J7200	Injection, factor IX, (antihemophilic factor, recombinant), Rixubis, per i.u.
J7201	Injection, factor IX, Fc fusion protein, (recombinant), Alprolix, 1 i.u.
J7202	Injection, factor IX, albumin fusion protein (recombinant), (Idelvion), 1 i.u.
J7203	Injection factor IX, (antihemophilic factor, recombinant), glycopegylated, (Rebinyn), 1 i.u.
J7204	Injection, factor viii, antihemophilic factor (recombinant), (esperoct), glycopegylated-exei, per iu
J7205	Injection, factor VIII Fc fusion protein (recombinant), per i.u.

HCPCS Code	Description
J7207	Injection, factor VIII, (antihemophilic factor, recombinant), pegylated, 1 i.u.
J7208	Injection, factor VIII, (antihemophilic factor, recombinant), pegylated-aucl, (Jivi), 1 i.u.
J7209	Injection, factor VIII (antihemophilic factor, recombinant), (Nuwiq), 1 i.u.
J7210	Injection, factor VIII, (antihemophilic factor, recombinant), (Afstyla), 1 i.u.
J7211	Injection, factor VIII, (antihemophilic factor, recombinant), (Kovaltry), 1 i.u.
J7212	Factor VIIa (antihemophilic factor, recombinant)-jncw (Sevenfact), 1 mcg
J7213	Injection, coagulation factor IX (recombinant), Ixinity, 1 IU
J7214	Injection, Factor VIII/von Willebrand factor complex, recombinant (Altuviiio), per Factor VIII IU

Diagnosis Code	Description
D66	Hereditary factor VIII deficiency
D67	Hereditary factor IX deficiency
D68.00	Von Willebrand's disease, unspecified
D68.01	Von Willebrand disease, type 1
D68.020	Von Willebrand disease, type 2A
D68.021	Von Willebrand disease, type 2B
D68.022	Von Willebrand disease, type 2M
D68.023	Von Willebrand disease, type 2N
D68.029	Von Willebrand disease, type 2, unspecified
D68.03	Von Willebrand disease, type 3
D68.04	Acquired von Willebrand disease
D68.09	Other von Willebrand disease
D68.2	Hereditary deficiency of other clotting factors
D68.311	Acquired hemophilia
D69.1	Qualitative platelet defects

Background

Factor VIIa (FVIIa) is a vitamin K-dependent glycoprotein made up of 406 amino acid residues, and is structurally similar to human plasma-derived factor VIIa. FVIIa promotes hemostasis by forming complexes with tissue factor and activating coagulation factors in the intrinsic pathway: factor X to factor Xa, and factor IX to factor IXa. Activated factor Xa, complexed with other factors, converts prothrombin to thrombin and fibrinogen to fibrin to form a hemostatic plug.

Factor XIII (FXIII) is a naturally occurring glycoprotein in plasma that promotes cross-linking of fibrin during the coagulation process, and protects the newly formed clot from fibrinolysis. FXIII is a proenzyme which is activated in the presence of calcium ion, to form activated factor XIIIa. The activated form is homodimeric, with only the A-subunit having intracellular activity. The B-subunit has no enzymatic activity and functions to stabilize the structure against proteolysis.

Coagulation factor XIII A-subunit is a recombinant human factor XIII-A(2) homodimer composed of 2 factor XIII A-subunits. Recombinant coagulation factor XIII A-subunit binds to free human factor XIII B-subunit and is activated by thrombin in the presence of calcium. Once activated, it increases the mechanical strength of fibrin clots, retards fibrinolysis, and enhances platelet adhesion to the site of injury in a dose-dependent manner.

Antihemophilic Factor VIII (FVIII) Human is a dried concentrate of Factor VIII derived from pooled human plasma. FVIII is the coagulant portion of the Factor VIII complex in plasma. FVIII acts as a co-factor for Factor IX to activate Factor X, ultimately causing the formation of thrombin and fibrin, promoting platelet aggregation and adhesion to damaged vascular endothelium.

Antihemophilic Factor VIII /von Willebrand Factor Complex (human) is a lyophilized concentrate of factor VIII and von Willebrand Factor, which facilitates the activation of factor X ultimately causing the formation of thrombin and fibrin promoting platelet aggregation and adhesion to damaged vascular endothelium.

Antihemophilic Factor (recombinant), FC Fusion Protein is a fusion protein that temporarily replaces the missing Coagulation Factor VIII needed for effective hemostasis. It contains the Fc 12 region of human immunoglobulin G1 (IgG1), which binds to the neonatal Fc receptor (FcRn). FcRn is part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by cycling them back into circulation and prolonging their plasma half-life.

Antihemophilic Factor (recombinant), Porcine Sequence temporarily replaces the inhibited endogenous factor VIII that is needed for effective hemostasis in patients with acquired hemophilia A.

Recombinant antihemophilic Factor VIII is not derived from human blood. It is a lyophilized preparation of factor VIII, which facilitates the activation of factor X ultimately causing the formation of thrombin and fibrin promoting platelet aggregation and adhesion to damaged vascular endothelium.

All forms of factor IX (FIX) achieve hemostasis through the same mechanism. A complex of factor VII and tissue factor (via the extrinsic coagulation pathway) and factor XIa (via the intrinsic pathway) activate factor IX which, in combination with factor VIII:C, activates factor X to Xa. Through this pathway, prothrombin is converted to thrombin which, in turn, converts fibrinogen to fibrin clot.

The exact mechanism of action of anti-inhibitor complex (AICC) is unknown. It may be related to one or more of the active clotting factors and their ability to bypass the factor VIII inhibitor. In vitro experiments suggest the possibility of a factor Xa–like substance; or a complex of FVIIIC:Ag, factor IXa, and phospholipid as the active principle, which is only minimally inhibited by an inhibitor.

Factor IX Fc fusion protein recombinant transiently replaces missing coagulation factor IX required to achieve hemostasis during bleeding episodes in patients with factor IX deficiency. The Fc region of the drug binds to the neonatal Fc receptor (FcRn). FcRn assists in the delay of lysosomal degradation of immunoglobulins by cycling them back into circulation and increasing their plasma half-life. Hemophilia B patients have a prolonged activated partial thromboplastin time (aPTT), which is an established test for the biological activity of factor IX; factor IX Fc fusion protein recombinant therapy shortens the aPTT over the effective dosing period.

Fibrinogen (coagulation factor I) is a soluble plasma glycoprotein and a physiological substrate of 3 enzymes: thrombin, factor XIIIa, and plasmin. Thrombin converts fibrinogen into fibrin. Fibrin is stabilized in the presence of calcium ions and by activated Factor XIII. Factor XIIIa induces cross-linking of fibrin polymers which result in the fibrin clot being more elastic and more resistant to fibrinolysis. The cross-linked fibrin is the end result of the coagulation cascade. Cross-linked fibrin is the end result of the coagulation cascade, and provides tensile strength to a primary hemostatic platelet plug and structure to the vessel wall.

Antihemophilic factor VIII (recombinant) pegylated is a temporarily replaces coagulation factor VIII, thereby providing hemostasis in patients with congenital hemophilia A. Pegylation of the parent molecule (antihemophilic factor VIII recombinant) extends the half-life via reduced binding to the factor VIII clearance receptor (LRP1).

Coagulation Factor IX (recombinant), albumin fusion protein, temporarily replaces absent coagulation Factor IX to provide adequate hemostasis. The recombinant albumin is fused with recombinant Factor IX to extend the half-life of Factor IX.

Coagulation Factor X (human) is converted from its inactive form to the active form (Factor Xa) and with Factor Va on the phospholipid surface forms a prothrombinase complex which activates prothrombin to thrombin in the presence of calcium ions. Thrombin acts upon soluble fibrinogen and Factor XIII to generate a cross-linked fibrin clot.

Von Willebrand factor (recombinant) reduces factor VIII clearance by acting as a carrier protein and protecting factor VIII from rapid proteolysis. It promotes hemostasis by mediating platelet adhesion to damaged vascular subendothelial matrix (e.g., collagen) and platelet aggregation.

Hemlibra (emicizumab-kxwh) is a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure binding factor IXa and factor X. It bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective hemostasis.

Altuviiio [antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl] temporarily replaces the missing coagulation factor VIII needed for effective hemostasis. Altuviiio has demonstrated 3- to 4-fold prolonged half-life relative to other standard and extended half-life FVIII products.

Hympavzi (marstacimab-hncq) is a human monoclonal IgG1 antibody directed against the Kunitz domain 2 (K2) of tissue factor pathway inhibitor (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).

Alhemo (concizumab-mtci) is a monoclonal antibody antagonist of endogenous TFPI. Through the inhibition of TFPI, concizumab-mtci acts to enhance 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. The effect of concizumab-mtci is not influenced by the presence of inhibitory antibodies to FVIII or FIX. There is no structural relationship or sequence homology between concizumab-mtci and FVIII or FIX and, as such, treatment with concizumab-mtci does not induce or enhance the development of direct inhibitors to FVIII or FIX.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

Clinical Evidence

Proven

Congenital Factor XIII Deficiency

In a multinational, open-label, single-arm, phase 3 trial, researchers evaluated the efficacy and safety of prophylactic treatment with recombinant FXIII (rFXIII) [Tretten] in congenital FXIII-A subunit deficiency. Forty-one patients ≥ 6 years of age (mean, 26.4; range, 7-60) with confirmed congenital FXIII-A subunit deficiency were enrolled into the trial which consisted of a 4-week run-in period, followed by a 52-week treatment period (visits 2-15) of monthly (28 ±2 days) IV doses of 35 i.u./kg of rFXIII. During the rFXIII treatment period, 5 bleeding episodes (all trauma induced) in 4 patients were treated with FXIII-containing products. Crude mean bleeding rate was significantly lower than the historic bleeding rate (0.138 vs 2.91 bleeds/patient/year, respectively) for on-demand treatment. Transient, non-neutralizing, low-titer anti-rFXIII antibodies (Abs) developed in 4 patients; however, this did not result in allergic reactions, changes in any bleeds requiring treatment, or changes in FXIII pharmacokinetics during the trial or follow-up. These non-neutralizing Abs declined below detection limits in all 4 patients despite further exposure to rFXIII or other FXIII-containing products. Researchers conclude that prophylactic treatment with rFXIII is safe and effective in preventing bleeding episodes in patients with congenital FXIII-A subunit deficiency.

Factor XIII concentrate (human) [Corifact] labeling included expanded information in regards to use of rFXIII for peri-operative treatment of bleeds. Out of the 41 patients included in the trial, 5 patients underwent surgical procedures (4 were elective and 1 was an emergency). Of the 4 elective surgeries, 3 patients received rFXIII prior to surgery (0 to 7 days prior to surgery) with no post-operative bleeding. One patient who received rFXIII 7 days prior to surgery experienced bleeding post-extraction of all four wisdom teeth. The bleeding was stopped four hours after the oral surgery with an additional dose of rFXIII (50% of the patient's routine dose). One patient who required emergency surgery was pre-treated with plasma.

Von Willebrand Disease (VWD)

Gill et al. conducted a prospective, open-label, multinational study which evaluated the safety, efficacy, and optimal dosing of a VWF/FVIII concentrate [Humate-P] in patients with von Willebrand disease (VWD) undergoing elective surgery and expected to require at least two consecutive days of perioperative treatment with a VWF/FVIII concentrate. Dosing of factor was based on VWF ristocetin cofactor (VWF:RCo) and FVIII pharmacokinetic assessments performed before surgery. The studied population was composed of 33 adults and 9 children who completed the PK infusion phase. Effective hemostasis was achieved in 91.4% (32/35) of subjects immediately after surgery. Reported median terminal VWF:RCo half-life was 11.7 h, and median incremental in vivo recovery was 2.4 i.u. dL(-1) per i.u. kg(-1) infused. Three patients developed major hemorrhage after the immediate postoperative period. Median VWF/FVIII concentrate loading doses ranged from 42.6 i.u. VWF:RCo kg(-1) (oral surgery) to 61.2 i.u. VWF:RCo kg(-1) (major surgery), with a median of

10 (range, 2-55) doses administered per patient. Eleven patients experienced a total of 25 postoperative bleeding events, most of which were categorized as mild (16) or moderate (8). Researchers conclude that the results of this trial indicate that this VWF/FVIII concentrate is safe and effective in the prevention of excessive bleeding during and after surgery in individuals with VWD.

Researchers conducted a prospective, open-label, multicenter, non-randomized study which evaluated the safety and efficacy of a factor VIII (FVIII)/VWF concentrate [Humate-P] when used in treatment regimens based on VWF:ristocetin cofactor (VWF:RCo) activity in subjects with VWD in which desmopressin was known or suspected to be inadequate in situations requiring urgent and necessary surgery. Thirty-nine eligible patients with 42 evaluable surgical treatment events were included. Researchers reported the median loading dose based upon VWF:RCo activity was 82.3 international units/kilogram (i.u. kg(-1); range 32.5-216.8 i.u. kg(-1)), and the median maintenance dose per infusion was 52.8 i.u. kg(-1) (range 24.2-196.5 i.u. kg(-1)) for a median of 3 days (range 1-50 days). The median number of infusions per event was 6 (range 1-67 infusions). A total of 55 adverse events (AEs) were reported in 24 (57.1%) of 42 surgical treatment events and 3 of those AE events (which included peripheral edema, extremity pain and pseudo-thrombocytopenia) were reported as potentially treatment-related. No serious drug-related AEs or thrombotic events were reported. Researchers concluded that this study supports the safety and efficacy of treatment with FVIII/VWF concentrate for the prevention of surgical hemorrhage in patients with VWD when administered in doses calculated in VWF:RCo units.

Forty-five patients with von Willebrand disease (VWD) who received on demand von Willebrand factor/coagulation factor VIII complex (human) [Wilate] were evaluated in prospective clinical trials. bleeding was successfully controlled in 84.1% (95% confidence interval (CI), 81.8% to 86.2%) of episodes (898 of 1068 episodes); additionally, bleeding was successfully controlled in 93% of episodes in the 25 patients with VWD type 3. Non-successful treatment of a bleeding episode was documented if any of the following criteria was met: 1) the episodes was also treated with another VWF-containing product (excluding whole blood); 2) the patient required a blood transfusion during the bleeding episode; 3) the daily dosage of FVIII/VWF complex was 50% or greater above the initial required dose during follow-up treatment (for bleeding episodes requiring more than one day of treatment); 4) except for cases of gastrointestinal bleeding, FVIII/VWF complex was required for more than 4 days for the treatment of severe bleeding, more than 3 days for the treatment of moderate bleeding, or more than 2 days for the treatment of minor bleeding; and 5) the final bleeding episode had a moderate or none efficacy rating. Overall, most bleeding episodes were treated with FVIII/VWF complex for 1 to 3 days; however, patients with gastrointestinal bleeding the duration could be up to 7 days.

Congenital Factor VII Deficiency, Acquired Factor VIII Deficiency, Hemophilia A With Inhibitors, and Hemophilia B With Inhibitors

Mariani et al conducted a multi-center, prospective, observational, web-based study protocol to collect and describe treatment modalities and outcomes in congenital FVII deficiency (STER [Seven Treatment Evaluation Registry]). Forty-one surgical operations (24 'major' and 17 'minor') were performed in 34 patients diagnosed with FVII deficiency and administered recombinant activated Factor VII (rFVIIa) [NovoSeven]. Bleeding occurred during three major interventions of orthopedic surgery; however, rFVIIa was administered at very low dose in each case. An antibody to FVII was observed in one patient who underwent multiple dental extractions. No thromboses were reported during the 30-d follow up period. Replacement therapy with rFVIIa for surgery in FVII deficient patients is effective and safe when minimally effective doses were used, which, during the period of maximum bleeding risk (the day of operation), was calculated (Receiver Operated Characteristic analysis) to be of at least 13 μg/kg/body weight per single dose and no less than three administrations.

Factor Mimetics for Hemophilia A

Mahlangu et al evaluated the use of emicizumab in persons who have hemophilia A without factor VIII inhibitors as prophylactic therapy in a phase 3, multicenter trial. The authors randomly assigned patients aged 12 years or older who had been receiving episodic treatment with factor VIII to receive a subcutaneous maintenance dose of emicizumab of 1.5 mg per kilogram of body weight per week (group A) or 3.0 mg per kilogram every 2 weeks (group B) or no prophylaxis (group C). The primary end point was the difference in rates of treated bleeding between patient groups. Participants who had been receiving factor VIII prophylaxis received emicizumab at a maintenance dose of 1.5 mg per kilogram per week (group D). For patients who participated in the noninterventional study, intraindividual studies were performed. One hundred fifty two patients enrolled in the study. The annualized bleeding rate was 1.5 events (95% confidence interval [CI], 0.9 to 2.5) in group A and 1.3 events (95% CI, 0.8 to 2.3) in group B, as compared with 38.2 events (95% CI, 22.9 to 63.8) in group C; thus, the rate was 96% lower in group A and 97% lower in group B ($p < 0.001$ for both comparisons). A total of 56% of the participants in group A and 60% of those in group B had no treated bleeding events, as compared with those in group C, who all had treated bleeding events. In the intraindividual comparison involving 48 participants, emicizumab prophylaxis resulted in an annualized bleeding rate that was 68% lower than the rate with previous factor VIII prophylaxis ($p < 0.001$). The most frequent adverse event was low-grade injection-site reaction. There were no thrombotic or thrombotic microangiopathy events, development of antidrug antibodies, or new development of factor VIII inhibitors.

The authors conclude that prophylaxis with emicizumab led to a significantly lower bleeding rate than no prophylaxis among persons with hemophilia A without inhibitors; more than half the participants who received prophylaxis had no treated bleeding events. In an intraindividual comparison, emicizumab therapy led to a significantly lower bleeding rate than previous factor VIII prophylaxis.

Factor Replacement Products for Hemophilia A

The safety, efficacy, and pharmacokinetics of Altuviiio [antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl] were evaluated in two multicenter, prospective, open-label clinical studies (one study in adults and adolescents ≥ 12 years of age and one pediatric study in children < 12 years of age in previously treated patients (PTPs) with severe hemophilia A (< 1% endogenous Factor VIII activity or a documented genetic mutation consistent with severe hemophilia A). All studies evaluated the efficacy of routine prophylaxis with a weekly dose of 50 IU/kg and determined hemostatic efficacy in the treatment of bleeding episodes and during perioperative management in subjects undergoing major or minor surgical procedures. The completed adult and adolescent study enrolled a total of 159 PTPs (158 male and 1 female subjects) with severe hemophilia A. Subjects were aged 12 to 72 years and included 25 adolescent subjects aged 12 to 17 years. All 159 enrolled subjects received at least one dose of Altuviiio and were evaluable for efficacy. A total of 149 subjects (93.7%) completed the study. The ongoing pediatric study enrolled 67 male PTPs. The efficacy of weekly 50 IU/kg Altuviiio as routine prophylaxis was evaluated as estimated by the mean annualized bleed rate (ABR) and by comparing the ABR during on-study prophylaxis vs. the ABR during pre-study FVIII prophylaxis. A total of 133 adults and adolescents, who were on pre-study FVIII prophylaxis, were assigned to receive Altuviiio for routine prophylaxis at a dose of 50 IU/kg IV once weekly for 52 weeks (Arm A). An additional 26 subjects, who were on pre-study episodic (on-demand) treatment with FVIII, received episodic (on-demand) treatment with Altuviiio at doses of 50 IU/kg IV for 26 weeks, followed by routine prophylaxis at a dose of 50 IU/kg IV once weekly for 26 weeks (Arm B). Overall, 115 subjects received at least a total number of 50 exposure days (EDs) in Arm A and 17 subjects completed at least 25 EDs of routine prophylaxis in Arm B. Routine prophylaxis resulted in a mean ABR (95% CI) of 0.7 (0.5, 1.0), a median (Q1, Q3) ABR of 0 (0, 1.0), and a median (Q1, Q3) annualized joint bleeding rate of 0 (0, 1.0). An intra-subject comparison (n = 78) between mean ABR during on-study prophylaxis with Altuviiio and that during pre-study FVIII prophylaxis yielded a 77% reduction in treated bleeds (95% CI: 58%, 87%). All subjects with target joints at baseline (defined as ≥ 3 spontaneous bleeding episodes in a major joint which occurred in a consecutive 6-month period) achieved resolution of all target joints (45/45, 100%) with 12 months of prophylactic treatment with Altuviiio (defined as ≤ 2 bleeding episodes in the target joint in 12 months). The efficacy of weekly 50 IU/kg Altuviiio as routine prophylaxis in children < 12 years was evaluated as estimated by the mean annualized bleed rate (ABR). At the time of the interim analysis, a total of 67 children (31 children < 6 years of age and 36 children 6 to < 12 years of age) were enrolled to receive Altuviiio for routine prophylaxis at a dose of 50 IU/kg IV once weekly for 52 weeks. In subjects with at least 26 weeks of exposure (n = 23), routine prophylaxis resulted in a mean ABR (95% CI) of 0.5 (0.2, 1.3) and a median (Q1, Q3) ABR of 0 (0, 1.3) for treated bleeds. For all bleeds (treated and non treated), the mean ABR (95% CI) was 3.6 (1.6, 8.4) and the median (Q1, Q3) ABR was 0 (0, 4.5). In the adult and adolescent study, a total of 362 bleeding episodes were treated with Altuviiio, most occurring during on-demand treatment in Arm B. Majority of bleeding episodes were localized in joints. Response to the first injection was assessed by subjects at least 8 hours after treatment. A 4-point rating scale of excellent, good, moderate, and no response was used to assess response. Bleeding was resolved with a single 50 IU/kg injection of Altuviiio in 96.7% of bleeding episodes. The median (Q1; Q3) total dose to treat a bleeding episode was 50.9 IU/kg (50.0; 51.9). Control of bleeding episodes was similar across the treatment arms. Perioperative hemostasis was assessed in 13 major surgeries in 12 subjects (11 adults and 1 child). Of the 13 major surgeries, 12 surgeries required a single pre-operative dose to maintain hemostasis during surgery; for 1 major surgery during routine prophylaxis no pre-operative loading dose was administered on the day of/or before surgery. The median dose per preoperative injection was 49.96 IU/kg (range 12.7 - 61.9). The clinical evaluation of hemostatic response during major surgery was assessed using a 4-point scale of excellent, good, moderate, or poor/none. The hemostatic effect of Altuviiio was rated as “excellent” in 13 of 13 surgeries (100%). No surgery had an outcome rated as “poor/none” or “missing.” Types of major surgeries assessed include major orthopedic procedures such as joint arthroplasties (joint replacements of knee, hip, and elbow), joint revisions and ankle fusion. Other major surgeries included molar extractions and rhinoplasty/mentoplasty. Perioperative hemostasis was assessed in 22 minor surgeries in 19 subjects (12 adults and 7 children). The hemostatic response was evaluated by the investigator/surgeon in 15 of these minor surgeries; an excellent response was reported in all (100%).

Mahlangu et al. conducted a multi-center, prospective, open-label, phase 3 study which evaluated the safety, efficacy, and pharmacokinetics of a recombinant FVIII Fc fusion protein (rFVIIIFc) [Eloctate] for prophylaxis, treatment of acute bleeding, and perioperative hemostatic control in 165 previously treated males aged ≥ 12 years with severe hemophilia A. The study participants were divided up into 3 treatment arms: arm 1, individualized prophylaxis (25-65 i.u./kg every 3-5 days, n = 118); arm 2, weekly prophylaxis (65 i.u./kg, n = 24); and arm 3, episodic treatment (10-50 i.u./kg, n = 23). A subgroup compared recombinant FVIII (rFVIII) and rFVIIIFc pharmacokinetics. Annualized bleeding rate (ABR) was the primary measured outcome; and inhibitor development and adverse events were secondary efficacy endpoints evaluated. The terminal half-life of rFVIIIFc (19.0 hours) was extended 1.5-fold vs rFVIII (12.4 hours; p < .001). Across all arms, 757

bleeding episodes were treated with rFVIIIFc during the efficacy period. Overall, 87.3% of bleeding episodes were resolved with 1 injection, and 97.8% were controlled with ≤ 2 injections. In arm 1, the median weekly dose was 77.9 i.u./kg; approximately 30% of subjects achieved a 5-day dosing interval (last 3 months on study). Adverse events were representative of events occurring in the general hemophilia population and no participants developed inhibitors. The study was not designed to compare individualized and weekly prophylactic regimens (arms1 and 2, respectively). Thus, although both the individualized (median twice-weekly dosing) and weekly dosing regimens resulted in a significant reduction in ABR compared with episodic treatment, the superiority of one approach for prophylactic dosing over the other cannot be determined. Authors concluded that rFVIIIFc was well-tolerated and efficacious in the prevention and treatment of bleeding events, including within the setting of major surgery, in adolescents and adults with severe hemophilia A. Additionally, efficacy results supported the potential for rFVIIIFc dosing 1 to 2 times per week (current treatment guidelines recommend dosing 3-4 times weekly).

Three multi-center, open-label, non-controlled trials (n = 213) were conducted to evaluate the safety and efficacy of antihemophilic factor (recombinant) [Novoeight] in the control and prevention of breakthrough bleeds, routine prophylaxis, and perioperative management in previously treated patients with hemophilia A. Of the 213 patients included, 150 patients were 12 years or older and 63 patients were younger than 12 years of age with severe hemophilia A (factor VIII activity less than 1%) and no history of factor VIII inhibitors. The median annual bleeding rate for adults and children 16 years or older was 3.1 bleeds/year. All patients received routine prophylaxis with antihemophilic factor (recombinant); those 12 years or older received 20 to 50 international units/kg 3 times weekly or 20 to 40 international units/kg every other day. Those younger than 12 years of age received either 25 to 60 international units/kg 3 times weekly or 25 to 50 international units/kg every other day. More than 80% received the 3-times-per-week regimen. Bleeding episodes were treated according to the investigator's discretion, with a target factor VIII activity level greater than 0.5 international units/mL. Bleeding episodes and perioperative management with antihemophilic factor (recombinant) were considered successfully treated if the patient (home dosing) or investigator (supervised treatment) rated the response to treatment as excellent or good; moderate or none ratings were considered unsuccessful treatment. Bleeding episodes (89% mild/moderate; 62% spontaneous; 72% localized to joints) occurred 991 times in 158 patients, with 84% successfully treated and 1.7% having no response. Only 1 or 2 injections were necessary to treat 91% of the bleeding episodes. Of the 11 patients (age range, 14 to 55 years) undergoing surgical procedures, 10 of the procedures were major and 1 was minor (tooth extraction). Excellent or good efficacy ratings were given in all cases.

Valentino et al. conducted an open-label, multicenter trial which compared the effectiveness of two prophylactic treatment regimens with antihemophilic factor (recombinant), plasma/albumin free method (rAHF-PFM) [Advate], as well as between on-demand and prophylaxis treatments, in preventing bleeding in hemophilia A. Sixty-six previously on-demand-treated patients aged 7-59 years with FVIII levels ≤ 2% received 6 months of on-demand treatment and were then randomized to 12 months of either standard (20-40 i.u. kg(-1) every other day) or pharmacokinetic (PK)-tailored (20-80 i.u. kg(-1) every third day) prophylaxis, both regimens intended to maintain FVIII trough levels at or above 1%. The primary endpoint was differences in annualized bleeding rates (ABRs) between the two prophylaxis regimens. Secondary endpoint evaluated included differences in ABRs between patients first treated on-demand and then on prophylaxis. A total of 1640 bleeding episodes occurred in 66 of 66 subjects during the on-demand period, 104 episodes occurred in 19 out of 32 subjects during standard prophylaxis and 141 episodes in 25 out of 34 subjects during the PK-tailored prophylaxis. Twenty-two (33.3%) patients on prophylaxis treatment experienced no bleeding episodes, whereas none treated on-demand were free from an episode of bleeding. ABRs for the two prophylaxis regimens were comparable, however, the differences between on-demand and either prophylaxis were statistically significant ($p < 0.0001$): median (interquartile range [IQR]) ABRs were 43.9 (21.9), 1.0 (3.5), 2.0 (6.9) and 1.1 (4.9) during on-demand treatment, standard, PK-tailored and any prophylaxis, respectively. No differences in FVIII consumption or adverse event rates between prophylaxis regimens were noted. No patient developed FVIII inhibitors. Researchers concluded that the outcomes of this trial demonstrated comparable safety and effectiveness for two prophylaxis regimens and that prophylaxis significantly reduces bleeding compared with on-demand treatment. Additionally, PK-tailored prophylaxis offers an alternative to standard prophylaxis for the prevention of bleeding in hemophilia A.

In a single-arm study of adults and adolescents (n = 55) with hemophilia A, 84.2% of all bleeding episodes were successfully treated successfully with Wilate. Minor episodes accounted for 26.3% of all bleeding, moderate episodes for 56.1%, and major episodes for 17.5%; there were no life-threatening bleeding episodes. Only 1 dose of Wilate(R) was required in 63.2% of the bleeding episodes, 2 doses were required in 21.1% of episodes, 3 doses were required in 12.3% of episodes, and 4 or more doses were required in 3.6% of episodes. Mean Wilate dose was 34 international units/kg per dose. Successful treatment was defined as excellent, good, or moderate efficacy as assessed by the patient. Excellent efficacy was defined as abrupt pain relief and/or improvement in bleeding within 8 hours of a single dose, good efficacy was defined as definite pain relief and/or improvement in bleeding within 8 to 12 hours after dose and requiring up to 2 doses for resolution, and moderate efficacy was defined as probable or slight benefit within 12 hours of a dose and requiring more than 2 doses for resolution. The annualized bleeding rate for spontaneous bleeds in adults (n = 50) was

1.67 episodes/patient (median, 0; range, 0 to 11.76). The annualized bleeding rate for all types of bleeds was 2.39 episodes/patients (median, 0; range, 0 to 15.69) among adults. Patients were treated for 6 months with 20 to 40 international units/kg (mean, 32 international units/kg) every 2 to 3 days.

Factor Replacement Products for Hemophilia B

Powell et al conducted a phase 3, nonrandomized, open-label study which evaluated the safety, efficacy, and pharmacokinetics of coagulation factor IX Fc fusion protein recombinant (rFIXFc) [Alprolix] for prophylaxis, treatment of bleeding, and perioperative hemostasis in patients with severe factor IX deficiency (hemophilia B). Patients (age range, 12 to 71 years; n = 123) were evaluated in trials to determine hemostatic efficacy of rFIXFc for prophylaxis, treatment of bleeding, and perioperative management. In the fixed-interval prophylaxis arm, patients received an initial dose of 50 i.u./kg, which was then adjusted to maintain a factor IX trough level of at least 1% to 3% above baseline (median dose, 45.2 i.u./kg). Patients in the individualized-interval arm received rFIXFc 100 i.u./kg every 10 days, with the interval adjusted to maintain a factor IX trough of at least 1% to 3% above baseline (median dosing interval, 12.5 days). Patients in the episodic treatment arm received rFIXFc 20 to 100 i.u./kg as needed for bleeding. The primary efficacy end point was the annualized bleeding rate, and safety end points included the development of inhibitors and adverse events. A total of 636 bleeding episodes were assessed in 114 patients, who received a median total dose of 46.99 i.u. per bleeding episode. During a median follow-up of 51.4 weeks, the annualized bleeding rates were decreased by 83% in the fixed-weekly interval group and 87% in the individualized group compared with the episodic treatment group. Most bleeding episodes (90.4%) were treated with 1 dose; 97.3% required 1 or 2 injections. The median annualized overall bleeding rates were 2.95% in the fixed-interval prophylaxis group, 1.38% in the individualized-interval prophylaxis group, and 17.69% in the episodic treatment group. Researchers concluded that rFIXFc is safe and effective for the treatment and prevention of bleeding events, including those incurred during major surgeries, in previously treated adolescents and adults with hemophilia B. Fc fusion did not impair factor IX activity or result in increased immunogenicity. The prolonged half-life of rFIXFc allowed for effective prophylaxis, with injections every 1 to 2 weeks. Additionally, the potential for higher trough levels of rFIXFc or longer intervals between doses may lead to greater use of prophylaxis among patients with hemophilia B.

In a prospective, open-label, uncontrolled trial, efficacy of routine prophylaxis with coagulation factor IX [Rixubis] in adult patients with hemophilia B (n = 56) was evaluated. Primary endpoint was reduction in frequency of bleeding episodes. Patients received coagulation factor IX recombinant 40 to 60 international units/kg IV twice weekly for 3 months or longer. At screening, all patients had severe (factor IX level < 1%) or moderately severe (factor IX level ≤ 2%) hemophilia B, with 12 or more documented bleeding episodes requiring treatment within 12 months prior to enrollment. After a mean duration of 6 months of treatment with coagulation factor IX recombinant at a mean twice-weekly dose of 49.4 international units/kg/infusion, the mean total annualized bleeding rate was 4.3 for all bleeds, 1.7 for spontaneous bleeds, and 2.9 for joint bleeds compared with 33.9 +/- 17.37 mean total annualized bleeding rate in the on-demand arm (n = 14) during the mean 3.5-month period.

Rebalancing Agents for Hemophilia A and B

The efficacy of Alhemo (concizumab-mtci) was established in an open-label study in 91 adult and 42 adolescent male patients with hemophilia A or B with inhibitors who have been prescribed, or require, treatment with bypassing agents. The study included 52 patients previously treated on-demand, were randomized to no prophylaxis (arm 1: on demand treatment with bypassing agents) or Alhemo prophylaxis (arm 2). The estimated mean annualized bleeding rate (ABR) was 1.7 (95%CI: 1.01, 2.87) for patients on Alhemo prophylaxis and 11.8 (95%CI: 7.03; 19.86) for patients on no prophylaxis. A ratio of the ABR was estimated to 0.14 ($p < 0.001$), corresponding to a reduction in ABR of 86% for patients on Alhemo prophylaxis compared to no prophylaxis. Warnings and precautions for Alhemo include thromboembolic events and hypersensitivity reactions. The most common adverse reactions (≥ 5%) with Alhemo use were injection site reactions and urticaria.

The efficacy of Hympavzi (marstacimab-hncq) was established in the BASIS study, an open-label, two-phase study 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. Following screening, patients entered a 6-month observation phase and were enrolled in 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. The efficacy of Hympavzi for each cohort was based upon the annualized bleeding rate (ABR) of treated bleeds during treatment with Hympavzi compared to ABR during the observational phase. In the cohort of patients receiving on-demand factor-based therapy, the ABR was 38.00 during the observational 6-month period vs. 3.18 with Hympavzi prophylaxis treatment during the 12-month active treatment period (ratio 0.084, 95% CI: 0.059, 0.119; $p < 0.0001$). Hympavzi prophylaxis demonstrated superiority over on-demand factor-based therapy in incidences of treated bleeds. In the cohort of patients receiving routine factor-based prophylaxis, the ABR was 7.85 during the observational 6-month period vs. 5.08 with Hympavzi

prophylaxis treatment during the 12-month active treatment period (difference -2.77, 95% CI: -5.37, -0.16). Hympavzi prophylaxis demonstrated non-inferiority to routine prophylactic factor-based therapy as measured by ABR of treated bleeds. The most common adverse reactions (≥ 3%) with Hympavzi use were injection site reaction, headache, and pruritus.

Professional Societies

In October 2024, the National Hemophilia Foundation (NHF) released updated hemophilia treatment guidelines entitled Medical and Scientific Advisory Council (MASAC) Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders #290. A summary of the NHF recommendations for physicians treating patients with hemophilia A and B, von Willebrand Disease, and other congenital bleeding disorders are as follows:

Treatment of Patients With Hemophilia A		
Recombinant Factor VIII Concentrates	Advate	Treatment of choice in hemophilia A
	Kogenate FS	
	Kovaltry	
	NovoEight	
	Nuwiq	
	Recombinate	
	Xyntha	
Prolonged Half-Life Recombinant Factor VIII Concentrate	Adynovate	
	Afstyla	
	Altuviiio	
	Eloctate	
	Esperoct	
	Jivi	
Plasma-Derived Factor VIII Concentrates	Hemofil M	Recommended
Plasma-Derived Factor VIII / von Willebrand Factor	Alphanate	Recommended
	Humate-P	
	Koate-DVI	
Humanized bispecific FIXa- and FX- directed monoclonal antibody	Hemlibra	Recommended
Cryoprecipitate	Cryoprecipitate	Not recommended except in life- and limb-threatening emergencies when no factor VIII concentrate is available
Desmopressin	DDAVP Injection	Recommended for use in mild hemophilia A. Children < 2 years of age and patients with mild hemophilia A in whom desmopressin does not provide adequate Factor VIII levels should be treated with either recombinant or plasma-derived FVIII concentrates. Use with caution in pregnant women during labor and delivery.
Treatment of Patients With Hemophilia B		
Recombinant Factor IX Concentrate	BeneFIX	Treatment of choice in hemophilia B
	Ixinity	
	Rixubis	
Prolonged Half-Life Recombinant Factor IX Concentrate	Alprolix	
	Idelvion	
	Rebinyn	
Plasma-Derived Factor IX Concentrates	AlphaNine SD	Recommended

Treatment of Patients With von Willebrand Disease (VWD)		
Desmopressin	DDAVP Injection	Recommended for most persons with VWD Type 1. Some Type 2A patients may respond to DDAVP, however clinical testing should be done to determine whether DDAVP can be used. Do not use in children < 2 years of age. Use with caution in pregnant women during labor and delivery.
Recombinant von Willebrand Factor Concentrate	Vonvendi	Treatment of choice in von Willebrand disease. May be used to treat patients with type 2B and type 3 VWD; it can also be used in patients with types 1, 2A, 2M, and 2N VWD who are not responsive to DDAVP and in children < 2 years of age regardless of VWD type.
Plasma-Derived Factor VIII / von Willebrand Factor	Alphanate Humate-P Wilate	Recommended in certain types of vWD that do not respond to DDAVP (i.e., Type 2B VWD and Type 3 VWD), and for use in Type 1 or 2A VWD patients who have become transiently unresponsive to DDAVP and in surgical situations, especially in young under the age of 2 years. In certain patients, Koate-DVI may also be effective.
Cryoprecipitate	Cryoprecipitate	Not recommended except in life- and limb-threatening emergencies when VWD-containing factor VIII concentrate is not immediately available.
Treatment of Patients With Factor VII Deficiency		
Recombinant Factor VIIa Concentrate	NovoSeven RT	Recommended
Treatment of Patients With Inherited Hemophilia A and Inhibitors to Factor VIII		
Humanized bispecific FIXa- and FX- directed monoclonal antibody	Hemlibra	Recommended
Treatment of Patients With Inherited Hemophilia A or B and Inhibitors to Factor VIII or Factor IX		
Plasma-Derived Activated Prothrombin Complex Concentrate (aPCC)	FEIBA	Recommended, however, products are not interchangeable. Choice of product depends on multiple factors, including type of inhibitor (low- or high-responding), current titer of inhibitor, location of the bleed, and previous response to these products. For high-titer inhibitors, immune tolerance induction is the best option for inhibitor eradication. Do not exceed recommended doses to reduce the risk of thrombosis.
Recombinant Factor VIIa Concentrate	NovoSeven RT Sevenfact	
Treatment of Patients With Acquired Inhibitors to Factor VIII		
Recombinant Factor VIIa Concentrate	NovoSeven RT	Recommended
Recombinant Porcine Factor VIII Concentrate	Obizur	
Treatment of Patients With Factor XIII Deficiency		
Plasma-Derived Factor XIII Concentrate	Corifact	Recommended
Treatment of Patients With Factor XIII-A Subunit Deficiency		
Plasma-Derived Factor XIII-A Subunit Concentrate	Tretten	Recommended. It is not effective in those patients that lack FXIII-B subunit.
Treatment of Patients With Factor II or Factor X Deficiencies		
Plasma-Derived Prothrombin Complex Concentrates (pd-PCCs)	Profilnine	Recommended to treat patients with deficiencies of factors II and X. However, it should be noted that the content of these factors varies from lot to lot and product to product. Note the relative content of factors Profilnine (II > IX = X > VII).
Treatment of Patients With Factor I Deficiency		
Plasma-Derived Fibrinogen Concentrate	RiaSTAP Fibryga	Recommended for treatment of congenital hypofibrinogenemia and afibrinogenemia but not dysfibrinogenemia.

Treatment of Patients With Factor I Deficiency		
Cryoprecipitate	Cryoprecipitate	The only currently available product for dysfibrinogenemia. Not recommended in patients with afibrinogenemia except in life- and limb-threatening emergencies when fibrinogen concentrate is not immediately available.
Treatment of Patients With Factor X Deficiencies		
Plasma-Derived Factor X Concentrate	Coagadex	Recommended

The World Federation of Hemophilia developed 2020 guidelines which provides practical guidelines on the general management of hemophilia which is summarized below:

- For patients with hemophilia, the WFH does not express a preference for recombinant over plasma-derived clotting factor concentrates.
- For treatment of FIX deficiency in patients with hemophilia B, the WFH recommends a product containing only FIX rather than prothrombin complex concentrates (PCCs), which also contain other clotting factors, such as factors II, VII, and X, some of which may become activated during manufacture and may predispose the patient to thromboembolism.
- Pure FIX concentrates are recommended over prothrombin complex concentrates for hemophilia B patients requiring prolonged therapy at high doses, undergoing surgery, liver disease, previous thrombosis, or known thrombotic tendency, or concomitantly using drugs known to have thrombogenic potential.
- For patients with hemophilia A or B, there is no evidence for any clinical safety issues in persons with hemophilia to recommend a preference among the various mechanisms of action (e.g., PEGylation, Fc-fusion, albumin-fusion) used to extend the half-life of clotting factor concentrates.
- For people with hemophilia A with an inhibitor requiring treatment for acute bleeding complications or surgery, the WFH recommends that a bypassing agent be used.
- For patients with hemophilia B and an inhibitor with a history of anaphylaxis to FIX-containing clotting factor concentrates, recombinant activated factor VIIa must be administered as activated prothrombin complex concentrate cannot be used.
- The WFH recommends that patients with hemophilia with an inhibitor should be considered for regular prophylaxis to prevent bleeding events.
  For patients with hemophilia, the WFH strongly recommends the use of viral-inactivated plasma-derived or recombinant clotting factor concentrates in preference to cryoprecipitate or fresh frozen plasma which are not recommended due to concerns about the safety and quality.
- For patients with mild or moderate hemophilia A and carriers of hemophilia A, the WFH recommends considering desmopressin (DDAVP) as an option for treatment.
- For adults, the WFH recommends DDAVP not be used for more than 3 consecutive days and only under close supervision. If DDAVP is administered twice in a single day, subsequent daily dosing should be limited to once per day.
- For children under 2 years of age, the WFH alerts that DDAVP is contraindicated due to increased risk of seizures as consequences of water retention and hyponatremia.
- For patients at risk of cardiovascular disease or thrombosis, the WFH recommends that DDAVP should be used with caution due to the risk of thromboembolism and myocardial infarction.
- For patients with hemophilia, the WFH recommends that antifibrinolytics are a valuable alternative to use alone or as adjuvant treatment, particularly in controlling mucocutaneous bleeding (e.g., epistaxis, oral and gastrointestinal bleeding, and menorrhagia) and for dental surgery and eruption or shedding of teeth.
- For patients with hematuria, the WFH recommends against the use of antifibrinolytics, as it is contraindicated in these patients due to increased risk of obstructive uropathy.
- For patients with renal impairment, the WFH recommends reduced dosing of antifibrinolytics and close monitoring.
- For patients with hemophilia A or B with a severe phenotype (note that this may include patients with moderate hemophilia with a severe phenotype), the WFH strongly recommends that such patients be on prophylaxis sufficient to prevent bleeds at all times, but that prophylaxis should be individualized, taking into consideration patient bleeding phenotype, joint 82 WFH Guidelines for the Management of Hemophilia, 3rd edition status, individual pharmacokinetics, and patient self-assessment and preference.
- For pediatric patients with severe hemophilia A or B, the WFH recommends early initiation of prophylaxis with clotting factor concentrates (standard or extended half-life FVIII/FIX) or other hemostatic agent(s) prior to the onset of joint disease and ideally before age 3, in order to prevent spontaneous and break-through bleeding including hemarthroses which can lead to joint disease.

- For adolescents and adults with hemophilia who show evidence of joint damage and have not as yet been on prophylaxis, the WFH recommends commencing tertiary prophylaxis in order to reduce the number of hemarthroses, spontaneous and break-through bleeding, and slow down the progression of hemophilic arthropathy.
- For patients with severe phenotype hemophilia A or B on prophylaxis, the WFH recommends that patients/ caregivers be taught to maintain timely and accurate records of bleeding episodes and treatment and be followed in hemophilia treatment centers.
- For patients with newly diagnosed hemophilia A and B, the WFH recommends regular inhibitor screening at least every 6-12 months, and then annually.
- For patients with hemophilia A and B who receive clotting factor concentrate for more than 5 consecutive days, the WFH suggests inhibitor screening within 4 weeks of the last infusion and for those patients who have poor or no response to adequate clotting factor replacement therapy, or who have lower than expected factor recovery or half-life.
- For patients with hemophilia A and FVIII inhibitors who develop an acute bleed, the WFH recommends that treatment be based on whether the inhibitor is low-responding or high-responding.
- For patients with hemophilia A and inhibitors who have acute bleeds, the WFH recommends FVIII concentrate for those with low-responding inhibitors, and a bypassing agent (recombinant factor VIIa [rFVIIa] or activated prothrombin complex concentrate [aPCC]) for those with high-responding inhibitors.
- For patients with hemophilia A and high-responding FVIII inhibitors who undergo surgery or an invasive procedure, the WFH recommends bypass agent therapy (rFVIIa or aPCC) at the discretion of the clinician. If single-agent bypass fails, sequential bypass agent treatment, i.e., rFVIIa alternating with aPCC, is another therapeutic approach. The WFH also recommends close clinical monitoring for thrombosis.
- For patients with hemophilia B and inhibitors who develop an acute bleed, the WFH recommends treatment based on whether the inhibitor is low-responding or high-responding and whether there is a history of allergic reactions.
- For patients with hemophilia B and low-responding FIX inhibitors, the WFH recommends use of a FIX containing product to treat acute bleeds, as long as there is no allergic reaction to FIX.
- For patients with hemophilia B and high-responding FIX inhibitors, the WFH prefers rFVIIa over aPCC to treat acute bleeds, as aPCC contains FIX and may cause or worsen an allergic reaction.
- For patients with hemophilia B and low-responding FIX inhibitors who undergo surgery, the WFH has no preference for type of FIX products, but recommends more frequent dosing due to the short FIX half-life.
- For patients with hemophilia B and FIX inhibitors who undergo surgery, the WFH recommends rFVIIa over aPCC, as aPCC contains FIX and may cause or worsen an allergic reaction.
- For patients with hemophilia A or B who switch to another type or brand of factor product, the WFH has no preference in the choice of specific type of therapy, as current evidence indicates product switching does not increase the risk of inhibitor development, but rigorous controlled trials are lacking.

The American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH) released an updated guidelines entitled 2021 Guidelines on the Management of von Willebrand Disease (VWD). A summary of the recommendations for the management of VWD is as follows:

- In patients with VWD with a history of severe and frequent bleeds, the guideline panel suggests using long-term prophylaxis rather than no prophylaxis.
- In patients for whom desmopressin is a valid treatment option (primarily type 1 VWD) and who have a baseline VWF level of < 0.30 IU/mL, the panel suggests performing a trial of desmopressin and treating based on the results over not performing a trial and treating with tranexamic acid or factor concentrate.
- In these patients, the pane suggests against treating with desmopressin in the absence of desmopressin trial results.
- In patients with VWD and cardiovascular disease who require treatment with antiplatelet agents or anticoagulant therapy, the panel suggests giving the necessary antiplatelet or anticoagulant therapy over no treatment.
- The panel suggests targeting both FVIII and VWF activity levels of ≥ 0.50 IU/mL for at least 3 days after surgery.
- The panel suggests against using only FVIII ≥ 0.50 IU/mL as a target level for at least 3 days after surgery.
- In patients undergoing minor surgery or minor invasive procedures, the panel suggests increasing VWF activity levels to ≥ 0.50 IU/mL with desmopressin or factor concentrate with the addition of tranexamic acid over raising VWF levels to ≥ 0.50 IU/mL with desmopressin or factor concentrate alone.
- The panel suggests giving tranexamic acid alone over increasing VWF activity levels to ≥ 0.50 IU/mL with any intervention in patients with type 1 VWD with baseline VWF activity levels of > 0.30 IU/mL and a mild bleeding phenotype undergoing minor mucosal procedures.
- The panel suggests using either hormonal therapy (combined hormonal contraception [CHC] or levonorgestrel-releasing intrauterine system) or tranexamic acid over desmopressin to treat women with VWD with heavy menstrual bleeding who do not wish to conceive.

- The panel suggests using tranexamic acid over desmopressin to treat women with VWD and heavy menstrual bleeding who wish to conceive.
- In women with VWD for whom neuraxial anesthesia during labor is deemed suitable, the panel suggests targeting a VWF activity level of 0.50 to 1.50 IU/mL over targeting an activity level of > 1.50 IU/mL to allow neuraxial anesthesia.
- The guideline panel suggests the use of tranexamic acid over not using it in women with type 1 VWD or low VWF levels (and this may also apply to types 2 and 3 VWD) during the postpartum period).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Advate [antihemophilic factor (recombinant)] is approved by the U.S. Food and Drug Administration (FDA) for use in children and adults with hemophilia A for the following: control and prevention of bleeding episodes; perioperative management; and routine prophylaxis to prevent or reduce the frequency of bleeding episodes. Advate is not indicated for the treatment of von Willebrand disease.

Adynovate [antihemophilic factor (recombinant), PEGylated] is FDA-labeled in children and adults with hemophilia A (congenital factor VIII deficiency) for the following: on-demand treatment and control of bleeding episodes; perioperative management; and routine prophylaxis to reduce the frequency of bleeding episodes. Adynovate is not indicated for the treatment of von Willebrand disease.

Afstyla [antihemophilic factor (recombinant)] is FDA-labeled in adults and children with hemophilia A (congenital Factor VIII deficiency) for the following: on-demand treatment and control of bleeding episodes; routine prophylaxis to reduce the frequency of bleeding episodes; and perioperative management of bleeding. Afstyla is not indicated for the treatment of von Willebrand disease.

Alhemo (concizumab-mtci) is a tissue factor pathway inhibitor (TFPI) antagonist 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, or hemophilia B (congenital factor IX deficiency) with FIX inhibitors.

Alphanate [antihemophilic factor/von Willebrand factor complex (human)] is FDA-labeled for control and prevention of bleeding in adult and pediatric patients with hemophilia A. It is also approved for surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease in whom desmopressin (DDAVP) is either ineffective or contraindicated. Alphanate is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

AlphaNine SD [coagulation factor IX (human)] is FDA-labeled for the prevention and control of bleeding in patients with Factor IX deficiency due to hemophilia B. AlphaNine SD contains low, non-therapeutic levels of Factors II, VII, and X, and, therefore, is not indicated for the treatment of Factor II, VII or X deficiencies. This product is also not indicated for the reversal of coumarin anticoagulant-induced hemorrhage, nor in the treatment of hemophilia A patients with inhibitors to Factor VIII.

Alprolix [coagulation factor IX (recombinant), Fc fusion protein] is FDA-labeled in adults and children with hemophilia B for the following: on demand treatment and control of bleeding episodes; perioperative management of bleeding; and for routine prophylaxis to reduce the frequency of bleeding episodes. Alprolix is not indicated for induction of immune tolerance in patients with hemophilia B.

Altuviiio [antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl] is a recombinant DNA-derived, Factor VIII concentrate indicated for use in adults and children with hemophilia A (congenital factor VIII deficiency) for the following: routine prophylaxis to reduce the frequency of bleeding episodes; on-demand treatment & control of bleeding episodes; and perioperative management of bleeding. Altuviiio is not indicated for the treatment of von Willebrand disease.

BeneFIX [coagulation factor IX (recombinant)] is FDA-labeled for both control and prevention of bleeding episodes in adult and pediatric patients with hemophilia B, and for peri-operative management in adult and pediatric patients with hemophilia B. BeneFIX is not indicated for Induction of immune tolerance in patients with hemophilia B.

Coagadex [coagulation factor X (human)] is FDA-labeled in adults and children with hereditary Factor X deficiency for the following: routine prophylaxis to reduce the frequency of bleeding episodes, on-demand treatment, and control of bleeding

episodes; and perioperative management of bleeding in patients with mild, moderate, and severe hereditary Factor X deficiency.

Corifact [factor XIII concentrate (human)] is FDA-labeled in adult and pediatric patients with congenital Factor XIII deficiency for the following: routine prophylactic treatment and peri-operative management of surgical bleeding.

Eloctate [antihemophilic factor (recombinant), Fc fusion protein] is FDA-labeled in adults and children with hemophilia A for the following: on-demand treatment and control of bleeding episodes; perioperative management of bleeding; and routine prophylaxis to reduce the frequency of bleeding episodes. Eloctate is not indicated for the treatment of von Willebrand disease.

Esperoct [antihemophilic factor (recombinant), glycopegylated-exei] is a coagulation Factor VIII concentrate indicated for use in adults and children with hemophilia A for on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes. Esperoct is not indicated for the treatment of von Willebrand disease.

FEIBA (anti-inhibitor coagulant complex) is FDA-labeled in hemophilia A and B patients with inhibitors for the following: control and prevention of bleeding episodes; peri-operative management; and routine prophylaxis to prevent or reduce the frequency of bleeding episodes. FEIBA is not indicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to factor VIII or factor IX.

Fibryga is a human fibrinogen concentrate indicated for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. Fibryga is also indicated for fibrinogen supplementation in bleeding patients with acquired fibrinogen deficiency. Fibryga is not indicated for dysfibrinogenemia.

Hemlibra (emicizumab-kxwh) is a bispecific factor IXa- and factor X-directed antibody and is 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.

Hemofil M [antihemophilic factor (human)] is FDA-labeled for the prevention and control of hemorrhagic episodes in hemophilia A. Hemofil M is not indicated in von Willebrand disease.

Humate-P [antihemophilic factor/von Willebrand factor complex (human)] is FDA-labeled for treatment and prevention of bleeding in adults with hemophilia A. It is also indicated in adults and children with von Willebrand disease (VWD) for treatment of spontaneous and trauma-induced bleeding episodes, and for prevention of excessive bleeding during and after surgery. This includes patients with severe VWD as well as patients with mild to moderate VWD where the use of desmospressin is known or suspected to be inadequate. Humate-P is not indicated for the prophylaxis of spontaneous bleeding episodes in VWD.

Hympavzi (marstacimab-hncq) is a tissue factor pathway inhibitor (TFPI) antagonist 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.

Idelvion [coagulation factor IX (recombinant), albumin fusion protein] is FDA-labeled in children and adults with hemophilia B (congenital Factor IX deficiency) for the following: on-demand treatment and control of bleeding episodes; perioperative management of bleeding; and routine prophylaxis to prevent or reduce the frequency of bleeding episodes. Idelvion is not indicated for immune tolerance induction in patients with hemophilia B.

IXINITY [coagulation factor IX (recombinant)] is FDA-labeled for on—demand treatment and control of bleeding episodes and perioperative management in adults and children with hemophilia B. It is also indicated for routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia B. IXINITY is not indicated for induction of immune tolerance in patients with hemophilia B.

Jivi [antihemophilic factor (recombinant), PEGylated-aucl] is FDA-labeled for use in previously treated adults and adolescents (12 years of age and older) with hemophilia A (congenital Factor VIII deficiency) for on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes.

Koāte-DVI [antihemophilic factor (human)] is FDA-labeled for the treatment of hemophilia A in which there is a demonstrated deficiency of activity of the plasma clotting factor, Factor VIII, to control or prevent bleeding episodes, or in order to perform emergency and elective surgery on individuals with hemophilia. Koāte-DVI is not approved for the treatment of von Willebrand's disease.

Kogenate FS [antihemophilic factor (recombinant)] is FDA-labeled for the following: on-demand treatment and control of bleeding episodes in adults and children with hemophilia A; peri-operative management in adults and children with hemophilia A; routine prophylaxis to prevent or reduce the frequency of bleeding episodes in children with hemophilia A and to reduce the risk of joint damage in children without preexisting joint damage; and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults with hemophilia A. Kogenate FS is not indicated for the treatment of von Willebrand disease.

Kovaltry [antihemophilic factor (recombinant)] is FDA-labeled in adults and children with hemophilia A (congenital Factor VIII deficiency) for the following: on-demand treatment and control of bleeding episodes; perioperative management of bleeding; and routine prophylaxis to reduce the frequency of bleeding episodes. Kovaltry is not indicated for the treatment of von Willebrand disease.

Novoeight [antihemophilic factor (recombinant)] is FDA-labeled for the control and prevention of bleeding episodes in adults and children with hemophilia A. It is also indicated for peri-operative management and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A. Novoeight is not indicated for the treatment of von Willebrand disease.

NovoSeven RT [coagulation factor VIIa (recombinant)] is FDA labeled for the following: treatment of bleeding episodes in adults and children with hemophilia A or B with inhibitors and in adults with acquired hemophilia; perioperative management in adults and children with hemophilia A or B with inhibitors and in adults with acquired hemophilia; treatment of bleeding episodes and perioperative management in congenital Factor VII (FVII) deficiency; and treatment of Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets.[5]

Nuwiq [antihemophilic factor (recombinant)] is FDA-labeled in adults and children with hemophilia A for the following: on-demand treatment and control of bleeding episodes; perioperative management of bleeding; and routine prophylaxis to reduce the frequency of bleeding episodes. Nuwiq is not indicated for the treatment of von Willebrand disease.[41]

Obizur [antihemophilic factor (recombinant), porcine sequence] is FDA-labeled for the treatment of bleeding episodes in adults with acquired hemophilia A. Safety and efficacy of Obizur has not been established in patients with a baseline anti-porcine factor VIII inhibitor titer of greater than 20 BU. Obizur is not indicated for the treatment of congenital hemophilia A or von Willebrand disease.

Profilnine SD (factor IX complex) is FDA-labeled for the prevention and control of bleeding in patients with Factor IX deficiency due to hemophilia B. It is not indicated for use in the treatment of Factor VII deficiency.

Rebinyn [coagulation factor IX (recombinant), GlycoPEGylated] is FDA-labeled for use in adults and children with hemophilia B for on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes. Rebinyn is not indicated for immune tolerance induction in patients with hemophilia B.

Recombinate [antihemophilic factor (recombinant)] is FDA-labeled for use in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes. It is also indicated in the perioperative management of patients with hemophilia A (classical hemophilia). Recombinate is not indicated in von Willebrand's disease.

RiaSTAP [fibrinogen concentrate (human)] is FDA-labeled for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. RiaSTAP is not indicated for dysfibrinogenemia.

Rixubis [coagulation factor IX (recombinant)] is FDA-labeled for the following: treatment and control of bleeding episodes in adults and children with hemophilia B, peri-operative management of bleeding in adults and children with hemophilia B, and routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia B. Rixubis is not indicated for induction of immune tolerance in patients with hemophilia B.

Sevenfact [coagulation factor VIIa (recombinant)-jncw] is a coagulation factor VIIa concentrate indicated for the treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with hemophilia A or B with inhibitors. Limitation of use: Sevenfact is not indicated for treatment of congenital factor VII deficiency.

Tretten [coagulation factor XIII A-Subunit (recombinant)] is FDA-labeled for routine prophylaxis of bleeding in patients with congenital factor XIII A-subunit deficiency. It is not indicated for use in patients with congenital factor XIII B-subunit deficiency.

Vonvendi [von Willebrand factor (recombinant)] is FDA-labeled for on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes in patients with severe Type 3 von Willebrand disease receiving on-demand therapy in adults diagnosed with von Willebrand disease.

Wilate [von Willebrand factor (coagulation) factor VIII complex human] is FDA-labeled in children and adults with von Willebrand disease for the following: on-demand treatment and control of bleeding episodes and perioperative management of bleeding. Wilate is indicated in adolescents and adults with hemophilia A for routine prophylaxis to reduce the frequency of bleeding episodes and on-demand treatment and control of bleeding episodes.

Xyntha, Xyntha Solofuse [antihemophilic factor (recombinant), plasma/albumin-free] is FDA-labeled for treatment and control of bleeding episodes for perioperative management and for routine prophylaxis to reduce the frequency of bleeding episodes in patients with hemophilia A. Xyntha is not indicated in patients with von Willebrand disease.

References

1. Corifact® [package insert]. Kankakee, IL: CSL Behring LLC, September 2020.
2. Alphanate® [package insert]. Los Angeles, CA: Grifols Biologicals, Inc., November 2022.
3. Humate-P® [package insert]. Kankakee, IL: CSL Behring LLC, June 2020.
4. Wilate® [package insert]. Hoboken, NJ: Octapharma USA Inc., March 2020.
5. NovoSeven® RT [package insert]. Plainsboro, NJ: Novo Nordisk Inc., July 2020.
6. Hemofil M® [package insert]. Lexington, MA: Baxalta US Inc., March 2023.
7. Koāte® [package insert]. Fort Lee, NJ: Kedrion Biopharma, Inc., January 2022.
8. Advate® [package insert]. Lexington, MA: Baxalta US Inc., March 2023.
9. Kogenate® FS [package insert]. Whippany, NJ: Bayer HealthCare LLC, December 2019.
10. Recombinate® [package insert]. Lexington, MA: Baxalta US Inc., March 2023.
11. Xyntha® [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc., July 2022.
12. FEIBA® [package insert]. Lexington, MA: Baxalta US Inc., March 2023.
13. AlphaNine® SD [package insert]. Los Angeles, CA: Grifols Biologicals Inc., November 2022.
14. Profilnine® [package insert]. Los Angeles, CA: Grifols Biologicals Inc., March 2021.
15. BeneFIX® [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc., November 2022.
16. Peerschke E, Castellone D, Ledford-Kraemer M, et al. Laboratory Assessment of Factor VIII Inhibitor Titer The North American Specialized Coagulation Laboratory Association Experience. Am J Clin Pathol. 2009 Apr;131(4):552-8.
17. Fibryga® [package insert]. Paramus, NJ: Octapharma USA Inc., July 2024.
18. Inbal A, Oldenburg J, Carcao M, et al. Recombinant factor XIII: a safe and novel treatment for congenital factor XIII deficiency. Blood. 2012 May 31;119(22):5111-7.
19. Thompson A, Gill J, Ewenstein B, et al. Successful treatment for patients with von Willebrand disease undergoing urgent surgery using factor VIII/VWF concentrate (Humate-P). Haemophilia. 2004 Jan;10(1):42-51.
20. Mariani G, Dolce A, Batorova A, et al. Recombinant, activated factor VII for surgery in factor VII deficiency: a prospective evaluation - the surgical STER. Br J Haematol. 2011 Feb;152(3):340-6.
21. Gill J, Shapiro A, Valentino L, et al. von Willebrand factor/factor VIII concentrate (Humate-P) for management of elective surgery in adults and children with von Willebrand disease. Haemophilia. 2011 Nov;17(6):895-905.

22. Micromedex® 2.0, (electronic version). Truven Health Analytics, Greenwood Village, CO. Available at: http://www.micromedexsolutions.com. Accessed December 17, 2024.
23. Valentino L, Mamonov V, Hellmann A, et al. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. J Thromb Haemost. 2012 Mar;10(3):359-67.
24. RiaSTAP® [package insert]. Kankakee, IL: CSL Behring LLC, June 2021.
25. Rixubis® [package insert]. Lexinton, MA: Baxalta US Inc., March 2023.
26. Xyntha® Solofuse™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc., July 2022.
27. Novoeight® [package insert]. Plainsboro, NJ: Novo Nordisk Inc., July 2020.
28. Tretten® [package insert]. Plainsboro, NJ: Novo Nordisk Inc., June 2020.
29. Alprolix® [package insert]. Cambridge, MA: Biogen Inc., May 2023.
30. Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. N Engl J Med. 2013 Dec 12;369(24):2313-23.
31. Eloctate® [package insert]. Waltham, MA: Bioverativ Therapeutics Inc., May 2023.
32. Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood. 2014 Jan 16;123(3):317-25.
33. Obizur® [package insert]. Lexington, MA: Baxalta US, Inc., March 2023.
34. Ixinity® [package insert]. Seattle WA: Aptevo BioTherapeutics LLC, November 2022.
35. Kovaltry® [package insert]. Whippany, NJ: Bayer HealthCare LLC., December 2022.
36. Nuwiq® [package insert]. Hoboken, NJ: Octapharma USA, Inc., June 2021.
37. Afstyla® [package insert]. Kankakee, IL: CSL Behring LLC, June 2023.
38. Idelvion® [package insert]. Kankakee, IL: CSL Behring LLC, June 2023.
39. Adynovate® [package insert]. Lexington, MA: Baxalta US, Inc., August 2023.
40. Coagadex® [package insert]. Durham, NC: Bio Products Laboratory, May 2023.
41. Vonvendi® [package insert]. Lexington, MA: Baxalta US Inc., March 2023.
42. Hemlibra® [package insert]. South San Francisco, CA: Genentech, Inc., January 2024.
43. Jivi® [package insert]. Whippany, NJ: Bayer HealthCare LLC, August 2018.
44. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med. 2018; 379:811-22.
45. Rebinyn® [package insert]. Plainsboro, NJ: Novo Nordisk, Inc., August 2022.
46. Esperoct® [package insert]. Plainsboro, NJ: Novo Nordisk Inc., August 2022.
47. Sevenfact™ [package insert]. Louisville, KY: HEMA Biologics, November 2022.
48. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition [published correction appears in Haemophilia. 2021 Jul;27(4):699]. *Haemophilia*. 2020;26 Suppl 6:1-158. doi:10.1111/hae.14046.
49. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. *Blood Adv*. 2021;5(1):301-325. doi:10.1182/bloodadvances.2020003264.
50. Altuviiio™ [package insert]. Waltham, MA: Bioverativ Therapeutics Inc., March 2023.
51. von Drygalski A, Chowdary P, Kulkarni R, et al. Efanesoctocog Alfa Prophylaxis for Patients with Severe Hemophilia A. *N Engl J Med*. 2023;388(4):310-318. doi:10.1056/NEJMoa2209226.
52. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. MASAC Document #290. October 2, 2024.
53. Hympavzi™ [package insert]. New York, NY: Pfizer Inc., October 2024.
54. Alhemo® [package insert]. Plainsboro, NJ: Novo Nordisk Inc., December 2024.
55. Matsushita T, Shapiro A, Abraham A, et al. Phase 3 Trial of Concizumab in Hemophilia with Inhibitors. N Engl J Med. 2023;389(9):783-794. doi:10.1056/NEJMoa2216455.

Policy History/Revision Information

Date	Summary of Changes
06/01/2025	· New Medical Benefit Drug Policy

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.