CLOTTING FACTORS AND COAGULANT BLOOD PRODUCTS

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INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines 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.

CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership for New Jersey large and small groups, and New York lines of business.[4,5]
Benefit Type	Pharmacy[2] Medical[2,3]
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes[1]
Precertification with Medical Director Review Required	Yes[1]
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Other

Special Considerations	[1]Clotting Factor drugs do not require precertification, **except** for: • Self-administered clotting factor drugs provided by a Hemophilia Treatment Center which require review by a Medical Director or their designee, **and** • Eloctate under the medical benefit requires precertification through Oxford's Medical Management with review by a Medical Director or their designee. Self-administered Eloctate under the pharmacy benefit requires precertification through the PBM. • Precertification through Oxford's Medical Management is required for the assisted administration of **all** clotting factor drugs; refer to the policy titled Assisted Administration of Clotting Factors and Coagulant Blood Products. • For **Fibryga** and **Jivi**: Precertification is not required for Fibryga and Jivi however it is strongly recommended (if precertification is required as indicated above). While no penalty will be imposed for failure to request a pre-service review, if you do not request one, a medical necessity review will be conducted post-service to determine coverage. It is the referring physician's responsibility to provide medical documentation to demonstrate clinical necessity for the medication. As of **Feb. 1, 2019**, precertification will be required. [2]Self-administered clotting factors are covered in-network only under the **pharmacy benefit**, except for self-administered clotting factors provided by a Hemophilia Treatment Center which are covered under the medical benefit. [3]Assisted administration of clotting factors is covered under the medical benefit. [4]HMO Members: If drugs are requested or supplied through a non-par vendor and authorization is not approved, these services will not be reimbursed by Oxford. [5]For coverage of clotting factors and/or assisted administration of these drugs for Connecticut lines of business, refer to the policies titled Drug Coverage Guidelines and Home Health Care.

BENEFIT CONSIDERATIONS

Precertification is required for Eloctate under the medical benefit through Oxford's Medical Management, with review by a Medical Director or their designee. Refer to the policies titled Eloctate™ (Antihemophilic Factor (Recombinant), FC Fusion Protein) for Connecticut Lines of Business and Drug Coverage Guidelines.

Precertification is required for Eloctate under the pharmacy benefit through the Pharmacy Benefit Manager (PBM). Refer to the policy titled Drug Coverage Guidelines.

Precertification is required for all self-administered clotting factor drugs provided by a Hemophilia Treatment Center.

Precertification is required for assisted administration of clotting factors. Refer to the policy titled Assisted Administration of Clotting Factors and Coagulant Blood Products.

For coverage of clotting factor drugs and assisted administration of clotting factor drugs for Connecticut lines of business, refer to the policies titled Drug Coverage Guidelines and Home Health Care.

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Clotting factor drugs may be covered under the medical or pharmacy benefit. Please refer to the member specific benefit plan documents for additional information.

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 titled Acquired Rare Disease Drug Therapy Exception Process.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

This policy refers to the following products: [1-19,22,36-40,42,44,46-53,60]

Product Type	Specific Product
Factor VIIa (recombinant)	NovoSeven® RT [coagulation factor VIIa (recombinant)]
Factor XIII (plasma-derived)	Corifact®™ [factor XIII concentrate (human)]
Factor VIII (plasma-derived)	Hemofil M® [antihemophilic factor (human)]
	Koāte®-DVI [antihemophilic factor (human)]
	Monoclate-P® [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)]
	Helixate® FS [antihemophilic factor (recombinant)]
	Kogenate® FS [antihemophilic factor (recombinant)]
	Kovaltry® [antihemophilic factor (recombinant)]
	Novoeight® [antihemophilic factor (recombinant)]
	Nuwiq® [antihemophilic factor (recombinant)]
	Recombinate® [antihemophilic factor (recombinant)]
	Xyntha® [antihemophilic factor (recombinant)] Xyntha® Solofuse™ (antihemophilic factor (recombinant)]
Factor IX (plasma-derived)	AlphaNine® SD [coagulation factor IX (human)]
	Bebulin® [factor IX complex (human)]
	Mononine® [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]
Anti-Inhibitor Coagulant Complex (plasma-derived)	FEIBA® [anti-inhibitor coagulant complex (human)]

Product Type	Specific Product
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)]
	Eloctate® [antihemophilic factor (recombinant), Fc fusion protein]
	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)

The following information provides the indications and criteria for which specific clotting factors and coagulant blood products are considered proven and medically necessary. **Precertification is NOT required for clotting factor drugs except** for self-administered clotting factor drugs provided by a Hemophilia Treatment Center, and Eloctate under the medical benefit, which require review by a Medical Director or their designee.

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) [Alphanate or 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) [Wilate] is proven and medically necessary when both of the following criteria are met:
- Diagnosis of von Willebrand disease; **and**
- **One** of the following:
  - Treatment of bleeding episodes; or
  - Peri-operative management of surgical bleeding

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:

- 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**
  - Peri-operative management of surgical bleeding; **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, Koāte-DVI or Monoclate-P), and Factor VIII (recombinant) [Kogenate FS, Kovaltry, Novoeight, or Nuwiq] 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

Additional information to support medical necessity review:
Antihemophilic Factor (Recombinant) [Helixate] and Antihemophilic Factor (Recombinant), Pegylated [Adynovate, Jivi] are not medically necessary for treatment of hemophilia A for the following:
- Routine prophylactic treatment
- Peri-operative management of surgical bleeding
- Treatment of bleeding episodes

Published clinical evidence does not demonstrate superiority in efficacy and treatment adherence of Helixate, Jivi, or Adynovate to other available recombinant factor products.

Antihemophilic Factor (recombinant) [Advate or Recombinate] is proven for the treatment of hemophilia A.
Additional information to support medical necessity review:
Antihemophilic Factor (recombinant) [Advate or Recombinate] is medically necessary when all of the following criteria are met:
- Diagnosis of hemophilia A; **and**
- **One** of the following:
  - Submission of documentation showing failure to meet clinical goals (e.g., continuation of spontaneous bleeds, inability to achieve appropriate trough level) after a trial of **three** of the following recombinant factor products:
    - Kogenate FS
    - Kovaltry
    - NovoEight
    - Nuwiq

    or
  - Submission of documentation showing history of hypersensitivity to **three** of the following recombinant factor products:
    - Kogenate FS
    - Kovaltry
    - NovoEight
    - Nuwiq

  or
- Patient is currently on Advate or Recombinate therapy and meets **one** of the following criteria:
  - Patient has **not** received a manufacturer supplied sample at no cost in prescriber office or a 30 day free trial from a pharmacy as a means to establish as a current user of Advate or Recombinate; **or**
  - **Both** of the following:
    - Patient has received a manufacturer supplied sample at no cost in prescriber office or a 30 day free trial from a pharmacy as a means to establish as a current user of Advate or Recombinate; **and**
    - **One** of the following:
      - Submission of documentation showing failure to meet clinical goals (e.g., continuation of spontaneous bleeds, inability to achieve appropriate trough level) after a trial of **three** of the following recombinant factor products:

- Kogenate FS
- Kovaltry
- NovoEight
- Nuwiq

or

- Submission of documentation showing history of hypersensitivity to **three** of the following recombinant factor products:
  - Kogenate FS
  - Kovaltry
  - NovoEight
  - Nuwiq

Antihemophilic Factor (recombinant) [Xyntha] is proven for the treatment of hemophilia A.
Additional information to support medical necessity review:
Antihemophilic Factor (recombinant) [Xyntha] is medically necessary 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:
  - Submission of documentation showing failure to meet clinical goals (e.g., continuation of spontaneous bleeds, inability to achieve appropriate trough level) after a trial of **three** of the following recombinant factor products:
    - Kogenate FS
    - Kovaltry
    - NovoEight
    - Nuwiq

    or
  - Submission of documentation showing history of hypersensitivity to **three** of the following recombinant factor products:
    - Kogenate FS
    - Kovaltry
    - NovoEight
    - Nuwiq

  or
- **All** of the following:
  - Patient is currently on Xyntha; **and**
  - **One** of the following:
    - Submission of documentation showing failure to meet clinical goals (e.g., continuation of spontaneous bleeds, inability to achieve appropriate trough level) after a trial of **three** of the following recombinant factor products:
      - Kogenate FS
      - Kovaltry
      - NovoEight
      - Nuwiq

      or
    - Submission of documentation showing history of hypersensitivity to **three** of the following recombinant factor products:
      - Kogenate FS
      - Kovaltry
      - NovoEight
      - Nuwiq

      or
    - Physician attestation that patient would preferentially benefit from **Xyntha** on **one** of the following:
      - Patient is at high risk for the development of inhibitors (e.g., family history of inhibitors and success with product, current treatment less than 50 days, high risk genetic mutation, history of initial intensive therapy greater than 5 days)
      - Patient has developed inhibitors
      - Patient has undergone immune tolerance induction/immune tolerance therapy

Antihemophilic Factor (recombinant), FC Fusion Protein [Eloctate] is proven and medically necessary 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
- Prescribed dosage and interval utilized is within range as defined by the prescribing information

Additional information to support medical necessity review:

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

- **All** of the following:
  - Diagnosis of severe hemophilia A; **and**
  - Patient is not a suitable candidate for treatment with shorter half-life Factor VIII (recombinant) products [e.g., Kogenate FS, Kovaltry, Novoeight, or Nuwiq] as attested by the prescribing physician; **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 IU/kg
      - Infusing no more frequently than every 4 days

      or
    - Requested dosage regimen does not exceed 12.5 IU/kg/day

  or
- **All** of the following:
  - **One** of the following:
    - **Both** of the following:
      - Moderate hemophilia A
      - Endogenous factor VIII level 2% < 5% (0.02 IU/ml to less than 5 IU/ml)

      or
    - **Both** of the following:
      - Mild hemophilia A
      - Endogenous factor VIII level > 5% (greater than 0.05 IU/ml)

    and
  - Patient is not a suitable candidate for treatment with shorter half-life Factor VIII (recombinant) products [e.g., Kogenate FS, Kovaltry, Novoeight, or Nuwiq] as attested by the prescribing physician; **and**
  - **One** of the following:
    - Treatment of bleeding episodes
    - Prevention of bleeding in surgical interventions or invasive procedures (e.g., surgical prophylaxis)
    - Prevention of bleeding episodes (i.e., routine prophylaxis) with documentation of **one** of the following in an 8 week period:
      - ≥1 or more episodes of spontaneous/ traumatic bleeding into joint
      - ≥1 episode of spontaneous / traumatic bleeding into the central nervous system
      - ≥1 episode of severe soft tissue bleeding (i.e., ileopsoas)

    and
  - Documentation of **both** of the following:
    - Dose does not exceed 50 IU/kg
    - Infusing no more frequently than every 4 days

Antihemophilic Factor (recombinant), Single Chain [Afstyla] 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**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

Additional information to support medical necessity review:

Antihemophilic Factor (recombinant), Single Chain [Afstyla] is medically necessary for the treatment of Hemophilia A when all of the following criteria are met:

- Diagnosis of hemophilia A; **and**
- Patient is not a suitable candidate for treatment with shorter acting half-life Factor VIII (recombinant) products [Kogenate FS, Kovaltry, Novoeight, or Nuwiq] as attested by the prescribing physician; **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

Emicizumab-kxwh [Hemlibra] is proven and medically necessary when all of the following criteria are met (please note that emicizumab-kxwh [Hemlibra] is a self-injectible medication that should be obtained under the member's pharmacy benefit **unless** the following criteria are met):

- 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); **and**
- **One** of the following:
  - Patient is less than 7 years of age; **or**
  - Patient is 7 years of age or older and cannot self-inject and does not have a caretaker who can be trained to administer emicizumab-kxwh

Anti-Inhibitor Coagulant Complex (plasma-derived) [FEIBA] and Factor VIIa (recombinant) [NovoSeven RT] are 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] 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

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

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

- Diagnosis of hemophilia B; **and**
- Prevention and 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 must be met:

- Diagnosis of hemophilia B; **and**
- **One** of the following:
  - Control and prevention of bleeding episode; **or**
  - Prevention of bleeding in surgical interventions (i.e., surgical prophylaxis)

Additional information to support medical necessity review:

Coagulation Factor IX (Recombinant) [Ixinity] is not medically necessary for treatment of hemophilia B for the following:

- Control and prevention of bleeding episodes
- Peri-operative management
- Routine prophylaxis of to prevent or reduce the frequency of bleeding episodes.

Published clinical evidence does not demonstrate superiority in efficacy and treatment adherence of Ixinity to other available recombinant factor products.

Anti-Inhibitor Coagulant Complex (plasma-derived) [FEIBA] and Factor VIIa (recombinant) [NovoSeven RT] are proven and medically necessary when all of the following criteria must be 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

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

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

- Diagnosis of congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia; **and**
- **One** of the following:
  - Routine prophylactic treatment; **or**
  - Peri-operative management of surgical bleeding; **or**
  - Treatment of bleeding episodes

Glanzmann Thrombasthenia

Factor VIIa (recombinant) [NovoSeven RT] is proven and medically necessary when all of the following criteria must be 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:
  - Treatment of bleeding episodes; **or**
  - Peri-operative management of surgical bleeding

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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.[9]

Adynovate (antihemophilic factor (recombinant), PEGylated) is FDA-labeled in adolescent and adult patients (12 years and older) 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.[51]

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.[49]

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.[2]

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.[15]

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.[40]

Bebulin (factor IX complex) is FDA-labeled for the prevention and control of bleeding episodes in adult patients with hemophilia B. Bebulin is not indicated for use in the treatment of Factor VII deficiency. No clinical studies have been conducted to show benefit from this product for treating deficiencies other than Factor IX deficiency.[16]

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 the treatment of other factor deficiencies (e.g., factors II, VII, VIII, and X), hemophilia A patients with inhibitors to factor VIII, reversal of coumarin-induced anticoagulation, and bleeding due to low levels of liver-dependent coagulation factors. [19]

Coagadex (coagulation factor X (human)) is FDA-labeled in adults and children (aged 12 years and above) with hereditary Factor X deficiency for the following: on-demand treatment and control of bleeding episodes; and perioperative management of bleeding in patients with mild hereditary Factor X deficiency. Perioperative management of bleeding in major surgery in patients with moderate and severe hereditary Factor X deficiency has not been studied.[52]

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.[1]

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.[42]

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.[14]

Fibryga is a human fibrinogen concentrate indicated for the treatment of acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. Fibryga is not indicated for dysfibrinogenemia.[22]

Helixate FS (antihemophilic factor (recombinant)) is FDA-labeled for the following: control and prevention 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 pre-existing joint damage; and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults with hemophilia A. Helixate FS is not indicated for the treatment of von Willebrand disease.[10]

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.[6]

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 with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.[60]

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.[3]

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.[50]

IXINITY (coagulation factor IX (recombinant)) is FDA-labeled for control and prevention of bleeding episodes in adults and children ≥ 12 years of age with hemophilia B. It is also indicated for perioperative management. IXINITY is not indicated for induction of immune tolerance in patients with hemophilia B.[46]

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.[61]

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.[7]

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.[11]

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.[47]

Monoclate-P (antihemophilic factor (human)) is FDA-labeled for treatment of hemophilia A. Monoclate-P is not effective in controlling the bleeding of patients with von Willebrand's disease.[8]

Mononine (coagulation factor IX (human)) is FDA-labeled for the prevention and control of bleeding in Factor IX deficiency, also known as hemophilia B or Christmas disease. It is not indicated in the treatment or prophylaxis of hemophilia A patients with inhibitors to Factor VIII. Mononine is not indicated for replacement therapy of clotting Factors II, VII and X. It is also not indicated in the treatment or reversal of coumarin-induced anticoagulation or in a hemorrhagic state caused by hepatitis-induced lack of production of liver dependent coagulation factors.[17]

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.[38]

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.[48]

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.[44]

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.[18]

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.[12]

RiaSTAP (fibrinogen concentrate (human) is FDA-labeled for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.[35]

Rixubis (coagulation factor IX (recombinant)) is FDA-labeled for the following: control and prevention of bleeding episodes in adults with hemophilia B; peri-operative management in adults with hemophilia B; and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults with hemophilia B. Rixubis is not indicated for induction of immune tolerance in patients with hemophilia B.[36]

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.[39]

Vonvendi (von Willebrand factor (recombinant)) is FDA-labeled for on-demand treatment and control of bleeding episodes and perioperative management of bleeding in adults diagnosed with von Willebrand disease.[53]

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 not indicated for treatment of hemophilia A.[4]

Xyntha, Xyntha Solofuse (antihemophilic factor [recombinant], plasma/albumin-free) is FDA-labeled for control and prevention of bleeding episodes in patients with hemophilia A and for perioperative management in patients with hemophilia A. It is not indicated in patients with von Willebrand disease.[13,37]

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.[5-29]

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.[1-29]

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.[29,39]

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.[7-8,29]

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.[2-4,29]

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. [42]

Antihemophilic Factor (recombinant), Porcine Sequence temporarily replaces the inhibited endogenous factor VIII that is needed for effective hemostasis in patients with acquired hemophilia A. [44]

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.[9-13, 29,37-38,47-49]

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.[15-19, 29,36,46]

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.[14,29]

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. [29,40]

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. [22,29,35]

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).[29,51,61]

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.[29,50]

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.[29,52]

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.[29,53]

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.[60]

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 may apply.

HCPCS Code	Description
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 IU
J7181	Injection, factor XIII A-subunit, (recombinant), per IU (Tretten)

HCPCS Code	Description
J7182	Injection, factor VIII, (antihemophilic factor, recombinant), (Novoeight), per IU
J7183	Injection, von Willebrand factor complex (human), Wilate, 1 IU VWF:RCO
J7185	Injection, factor VIII (antihemophilic factor, recombinant) (XYNTHA), per IU
J7186	Injection, antihemophilic factor VIII/von Willebrand factor complex (human), per factor VIII IU
J7187	Injection, von Willebrand factor complex (Humate-P), per IU VWF:RCO
J7188	Injection, Factor VIII (antihemophilic factor, recombinant), per IU
J7189	Factor VIIa (antihemophilic factor, recombinant), per 1 mcg
J7190	Factor VIII (antihemophilic factor, human) per IU
J7192	Factor VIII (antihemophilic factor, recombinant) per IU, not otherwise specified
J7193	Factor IX (antihemophilic factor, purified, nonrecombinant) per IU
J7194	Factor IX complex, per IU
J7195	Injection, factor IX (antihemophilic factor, recombinant) per IU, not otherwise specified
J7198	Antiinhibitor, per IU
J7199	Hemophilia clotting factor, not otherwise classified
J7200	Injection, factor IX, (antihemophilic factor, recombinant), Rixubis, per IU
J7201	Injection, factor IX, Fc fusion protein, (recombinant), Alprolix, 1 IU
J7202	Injection, factor ix, albumin fusion protein, (recombinant), Idelvion, 1 i.u.
J7205	Injection, Factor VIII Fc fusion protein (recombinant), per IU
J7207	Injection, factor VIII, (antihemophilic factor, recombinant), pegylated, 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.

ICD-10 Diagnosis Code	Description
D66	Hereditary factor VIII deficiency
D67	Hereditary factor IX deficiency
D68.0	Von Willebrand's disease
D68.2	Hereditary deficiency of other clotting factors
D68.311	Acquired hemophilia
D69.1	Qualitative platelet defects

CLINICAL EVIDENCE

Proven/Medically Necessary

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) in congenital FXIII-A subunit deficiency. [25,39] 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 IU/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.[1] 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.[28] 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 haemostasis 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 IU dL(-1) per IU kg(-1) infused. Three patients developed major hemorrhage after the immediate postoperative period. Median VWF/FVIII concentrate loading doses ranged from 42.6 IU VWF:RCo kg(-1) (oral surgery) to 61.2 IU 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.

Researcher 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.[26] 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 (IU kg(-1); range 32.5-216.8 IU kg(-1)), and the median maintenance dose per infusion was 52.8 IU kg(-1) (range 24.2-196.5 IU 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 haemorrhage 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.[4] 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]).[27] 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 extraction. 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.

Hemophilia A

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. [43] The study participants were divided up into 3 treatment arms: arm 1, individualized prophylaxis (25-65 IU/kg every 3-5 days, n=118); arm 2, weekly prophylaxis (65 IU/kg, n=24); and arm 3, episodic treatment (10-50 IU/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 IU/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. 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. [38] 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. [31] 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 IU kg(-1) every other day) or pharmacokinetic (PK)-tailored (20-80 IU 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.

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). [29,40-41] 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 IU/kg, which was then adjusted to maintain a factor IX trough level of at least 1% to 3% above baseline (median dose, 45.2 IU/kg). Patients in the individualized-interval arm received rFIXFc 100 IU/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 IU/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 IU 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.[36]

Two studies were conducted to provide coagulation factor IX (human) [Mononine] for treatment of hemophilia B subjects who required extensive Factor IX replacement for surgery, trauma, or spontaneous bleeding (73 unique subjects and eight subjects enrolled twice for a total of 81 subjects), as well as to evaluate the safety and efficacy of coagulation factor IX (human) treatment.[17] The overall mean recovery during treatment was determined to be 1.23 ± 0.42 IU/dL rise/IU/kg (K) (range = 0.59 to 2.92 K) among the 55 subjects included in recovery analyses in Study 1 and to be 1. 12 ± 0.52 K (range = 0.61 to 2.08 K) among 10 subjects included in these analyses in Study 2. Five (5/81,6%) subjects reported adverse events attributed to coagulation factor IX (human) across both studies. In these studies, 100 doses of coagulation factor IX (human) were administered at a range of 71 to 161 IU/kg to a total of 36 subjects. Sixty-seven of these infusions were the subject of recovery analyses. Mean recovery tended to decrease as the dose of coagulation factor IX (human) increased:1.09 ± 0.52 K at doses > 75-95 IU/kg (n=38), 0.98 ± 0.45 K at doses > 95-115 IU/kg (n=21), 0.70 ± 0.38 K at doses > 115-135 IU/kg (n=2), 0.67 K at doses > 135-155 IU/kg (n=1), and 0. 73 ± 0. 34 K at doses > 155 IU/kg (n=5). Among the 36 subjects who received these high doses, only one (2. 8%) reported an adverse experience with a possible relationship to coagulation factor IX (human). No thrombogenic complications were observed or reported.

Technology Assessments

As an update to the 2011 intervention review, the Cochrane Collaboration published a 2015 review which evaluated the effectiveness of recombinant Factor VIIa (containing no human proteins) as compared to concentrates derived from plasma for treating acute bleeding episodes in people with haemophilia with inhibitors. Researchers again concluded that although there is a need for further randomized controlled trials, both rFVIIa (NovoSeven®) and aPCC (FEIBA®) are similar in efficacy and safety. Additionally, the review suggested that researchers in the field define commonly agreed objective measures in order to enable the pooling of their results, thus increasing the power of comparisons.[23,54]

The Cochrane Collaboration also published an intervention review which evaluated the effectiveness of clotting factor concentrate prophylaxis in the management of people with hemophilia A or B in 2011.[24] Authors conclude that there is strong evidence from randomized controlled trials and observational trials that prophylaxis started early preserves joint function in children with hemophilia as compared to on-demand treatment. This effect is due to a consistent reduction in total bleeds and hemarthrosis and leads to a significant improvement in quality of life, however, treatment prophylaxis is linked to an increased factor usage and overall cost of therapy. There was insufficient evidence to show that treatment prophylaxis decreased bleeding and related complications in patients with existing joint damage. Randomized controlled trials are warranted to establish the best preventative regimen for these patients.

Professional Societies

National Hemophilia Foundation (NHF)

In April 2018, 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 #240.'[55] 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:

National Hemophilia Foundation (NHF) Hemophilia Treatment Guidelines		
Treatment of Patients with Hemophilia A		
Recombinant Factor VIII Concentrates	Advate	Treatment of choice in hemophilia A.
	Helixate FS	
	Kogenate FS	
	Kovaltry	
	NovoEight	
	Nuwiq	
	Recombinate	
	Xyntha	
Prolonged Half-Life Recombinant Factor VIII Concentrate	Adynovate	Treatment of choice in hemophilia A.
	Eloctate	
	Jivi	
Plasma-Derived Factor VIII Concentrates	Hemofil M	Recommended
	Monoclate-P	
Plasma-Derived Factor VIII/von Willebrand Factor	Alphanate	Recommended
	Humate-P	
	Koate-DVI	
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.
	Stimate Nasal Spray for Bleeding	
Treatment of Patients with Hemophilia B		
Recombinant Factor IX Concentrate	BeneFIX	Treatment of choice in hemophilia B.
	Ixinity	
	Rixubis	
Prolonged Half-Life Recombinate Factor IX Concentrate	Alprolix	
	Idelvion	
Plasma-Derived Factor IX Concentrates	AlphaNine SD	Recommended
	Mononine	
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.
	Stimate Nasal Spray for Bleeding	
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	Alphanate	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
	Humate-P	

National Hemophilia Foundation (NHF) Hemophilia Treatment Guidelines		
Factor	Wilate	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.
Treatment of Patients with von Willebrand Disease (VWD) *(continued)*		
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 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	
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 Acquired Inhibitors to Factor VIII		
Recombinant Factor VIIa Concentrate	NovoSeven RT	Recommended
Recombinant Porcine Factor VIII Concentrate	Obizur	
Treatment of Patients with Factor VII Deficiency		
Recombinant Factor VIIa Concentrate	NovoSeven RT	Recommended
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)	Bebulin	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 Bebulin (X>II>IX>VII) and Profilnine (II>IX=X>VII).
	Profilnine	
Treatment of Patients with Factor I Deficiency		
Plasma-Derived Fibrinogen Concentrate	RiaSTAP Fibryga	Recommended for treatment of congenital hypofibrinogenemia and afibrinogenemia but not dysfibrinogenemia.
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

World Federation of Hemophilia

The World Federation of Hemophilia developed 2013 guidelines which provides practical guidelines on the general management of hemophilia (level 1 corresponding to the strongest evidence and level 5 the weakest) as outlined below:[21]

- Prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function. (Level 2) In patients with repeated bleeding, particularly into target joints, short-term prophylaxis for 4–8 weeks can be used to interrupt the bleeding cycle. This may be combined with intensive physiotherapy or synoviorthesis. (Level 3)
- Prophylactic administration of clotting factor concentrates is advisable prior to engaging in activities with higher risk of injury. (Level 4) Preoperative assessment should include inhibitor screening and inhibitor assay, particularly if the recovery of the replaced factor is significantly less than expected. (Level 4)
- Patients with mild hemophilia A, as well as patients receiving intensive factor replacement for the first time, are at particular risk of inhibitor development and should be re-screened 4–12 weeks postoperatively. (Level 4)
- The WFH strongly recommends the use of viral-inactivated plasma-derived or recombinant concentrates in preference to cryoprecipitate or fresh frozen plasma (FFP) for the treatment of hemophilia and other inherited bleeding disorders. (Level 5)
- For treatment of FIX deficiency, a product containing only FIX is more appropriate than prothrombin complex concentrates, which also contain other clotting factors such as factors II, VII, and X, some of which may become activated during manufacture. Products containing activated clotting factors may predispose to thromboembolism. (Level 2) Whenever possible, the use of pure FIX concentrates is preferable for the treatment of hemophilia B as opposed to PCC. (Level 2)
- Cryoprecipitate is preferable to FFP for the treatment of hemophilia A and VWD. (Level 4) Due to concerns about the safety and quality of FFP, its use is not recommended, if avoidable. (Level 4)
- DDAVP may be the treatment of choice for patients with mild or moderate hemophilia A when FVIII can be raised to an appropriate therapeutic level because it avoids the expense and potential hazards of using a clotting factor concentrate. (Level 3) Although DDAVP is not licensed for use in pregnancy, there is evidence that it can be safely used during delivery and in the postpartum period in an otherwise normal pregnancy. Its use should be avoided in pre-eclampsia and eclampsia because of the already high levels of VWF. (Level 3)
- Regular treatment with tranexamic acid alone is of no value in the prevention of hemarthroses in hemophilia. (Level 4) It is valuable, however, in controlling bleeding from skin and mucosal surfaces (e.g., oral bleeding, epistaxis, menorrhagia). (Level 2) Tranexamic acid is particularly valuable in the setting of dental surgery and may be used to control oral bleeding associated with eruption or shedding of teeth. (Level 4)
- Management of bleeding in patients with inhibitors must be in consultation with a center experienced in their management. (Level 5) Choice of treatment product should be based on titer of inhibitor, records of clinical response to product, and site and nature of bleed. (Level 4) Patients with a low-responding inhibitor may be treated with specific factor replacement at a much higher dose, if possible, to neutralize the inhibitor with excess factor activity and stop bleeding. (Level 4) Patients with a history of a high responding inhibitor but with low titers may be treated similarly in an emergency until an anamnestic response occurs, usually in 3–5 days, precluding further treatment with concentrates that only contain the missing factor. (Level 4)

British Committee for Standards in Haematology

The British Committee for Standards in Haematology released updated inhibitor treatment guidelines in 2013 entitled, "Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia."[57] A summary of the recommendations for the management of inhibitors is outlined below. Designations for the quality of evidence (A – highest, C – lowest) and strength of recommendation (1 – strong, 2 – weak) are given at the end of each recommendation.

- Bleeds may be managed with large doses of FVIII/IX in low responders and FVIII inhibitor bypassing activity (FEIBA) or activated recombinant FVII (rFVIIa) in high responders. FVIII can be considered for major bleeds in high responding patients with low-titre antibodies. For low-responding patients with low-titre inhibitors it is better to increase the frequency of FVIII/FIX infusions rather than increase the dose (2C).
- Bleeds may be managed with large doses of FVIII/IX in low responders and FVIII inhibitor bypassing activity (FEIBA) or activated recombinant FVII (rFVIIa) in high responders. FVIII can be considered for major bleeds in high responding patients with low-titre antibodies. For low-responding patients with low-titre inhibitors it is better to increase the frequency of FVIII/FIX infusions rather than increase the dose (2C).
- Patients who have experienced allergic reactions to FIX should be treated with rFVIIa (1C).
- Single dose FEIBA (50-100 µg/kg), single high dose (270 µg/kg) rFVIIa or 1-3 standard doses (90 µg/kg) of rFVIIa are all treatment options for early haemarthroses (1B).
- Treatment of non-joint bleeds should be with FVIII/FIX or standard doses of FEIBA or rFVIIa until further data are available (2C).
- Tranexamic acid should be considered in all patients who are not receiving high doses of FEIBA (>200 iu/kg/d) but is especially important for mucosal bleeds (2C).
- Some bleeds, unresponsive to bypassing agents, may be successfully treated by removal of the inhibitor using plasmaphaeresis and immunoadsorption together with high dose FVIII/IX concentrate (2B).

- Combined treatment with rFVIIa and FEIBA should only be considered for life-or-limb-threatening bleeds unresponsive to either agent used alone (2C).

The guidelines also address recommendations for the prophylaxis for inhibitor patients:
- Prophylaxis with a bypassing agent should be considered in young children after the first haemarthosis to reduce the risk of arthropathy (2C).
- If prophylaxis is required in patients awaiting ITI, rFVIIa should be used (2C).
- Prophylaxis with bypassing agents in patients on ITI should undergo a trial reduction when FVIII recovery is measureable and stopped when the Bethesda titre is negative, assuming significant break-through bleeds do not result (2C).
- Prophylaxis may be considered in older patients with recurrent bleeds or progressive arthropathy (2C).
- The choice of product for prophylaxis should be considered on an individual basis, taking into account previous response to treatment, logistics of administration and cost (2C).
- If the initial regimen is unsuccessful, increasing the frequency of infusion is more likely to be effective than increasing the dose (2C).

American Society of Hematology

The American Society of Hematology released an updated reference guide entitled 2012 Clinical Practice Guideline on the Evaluation and Management of von Willebrand Disease (VWD) [32] which provides a summary of the 2007 von Willebrand Disease (VWD): Evidence-based Diagnosis and Management Guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). [33,56] A summary of the recommendations for the management of VWD is as follows:
- Therapeutic trial of DDAVP is recommended prior to use. VWF:RCo and FVIII activities should be measured at baseline and within 1 hour. Additional testing 2-4 hours after DDAVP should be considered to evaluate for shortened survival.
- Most type 1 VWD patients will respond to DDAVP, although patients with VWF:RCo < 10IU/dL and FVIII activity < 20 IU/dL are less likely to have a clinically significant response. In type 2 VWD, DDAVP will increase the VWF concentration, but the VWF dysfunction will still be present. In type 2B VWD, DDAVP may result in transient thrombocytopenia. Therefore, DDAVP should be used with caution in type 2 VWD.
- To avoid tachyphylaxis, DDAVP therapy is typically discontinued after 2 or 3 daily doses.
- Minor bleeding should be treated with intravenous or nasal DDAVP, if results of DDAVP trial support its use.
- In presence of inadequate DDAVP response, VWF concentrate should be used, with dosing primarily based on VWF:RCo units and secondarily on FVIII units.
- For patients with mild to moderate VWD undergoing oral surgery, antifibrinolytics combined with DDAVP are generally effective.
- For severe bleeding (e.g., intracranial, retroperitoneal) or major surgery prophylaxis, initial target VWF:RCo and Factor VIII activity levels should be >100 IU/dL, and levels >50 IU/dL should be maintained for at least 7-10 days. In all patients receiving VWF concentrate, clinicians should perform proper thrombotic-risk assessment and institute appropriate strategies to prevent thrombosis.

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
01/01/2019	• Updated list of applicable HCPCS codes to reflect annual code edits: ○ Added J7170 and J7177 ○ Removed Q9995 ○ Revised description for J7178 • Archived previous policy version PHARMACY 262.25 T2