Drug and Biologic Coverage Policy

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Clotting Factors and Antithrombin

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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

The Clotting Factors and Antithrombin coverage policy includes the following products:

- **Antithrombin III**
  - **Human plasma-derived:** Thrombate III®
  - **Recombinant:** ATryn®
- **Anti-Inhibitor Coagulant Complex:** FEIBA™
- **Coagulation Factor X, (human):** Coagadex®
- **Emicizumab-kxwh:** Hemlibra®
- **Factor VIIa:** NovoSeven® RT
- **Factor VIII - Antihemophilic factor**
  - **Human plasma-derived:** Hemofil® M, Koate®
  - **Recombinant:** Advate®, Kogenate® FS, Novoeight®, Nuwiq®, Recombinate®, Xyntha®
  - **Recombinant, Fc fusion protein:** Eloctate®
  - **Recombinant, human DNA sequence derived:** Kovaltry®
  - **Recombinant, glycoPEGylated:** Esperoct®
  - **Recombinant, pegylated:** Adynovate™, Jivi®
  - **Recombinant, porcine sequence:** Obizur™
  - **Recombinant, single chain:** Afstyla®
- **Factor VIII-Antihemophilic factor/von Willebrand factor complex (human):** Alphanate®, Humate-P®
- **Factor IX**

  - **Human plasma-derived:** AlphaNine® SD, Mononine®
  - **Complex (human plasma-derived):** Profilnine®
  - **Recombinant:** BeneFIX®, Ixinity®, Rixubis™
  - **Recombinant, albumin fusion protein:** Idelvion®
  - **Recombinant, glycoPEGylated:** Rebinyn®
  - **Recombinant, Fc fusion protein:** Alprolix®
- **Factor XIII**
  - **Concentrate (human plasma-derived):** Corifact®
  - **Recombinant (Coagulation Factor XIII A-Subunit):** Tretten®
- **Fibrinogen concentrate:** RiaSTAP®, Fibryga®
- **von Willebrand factor, recombinant:** Vonvendi™
- **von Willebrand factor/coagulation factor VIII complex (human plasma-derived):** Wilate®

NOTE: Each Clotting Factor product has unique indications and uses and are only approved for use as listed in the criteria below.

Clotting Factor products are considered medically necessary when the following criteria are met:

Product	Criteria for Use
Advate (factor VIII, recombinant)	Individual with factor VIII deficiency (hemophilia A) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
Adynovate (factor VIII - antihemophilic factor [recombinant], pegylated)	Individual with factor VIII deficiency (hemophilia A) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
Afstyla (antihemophilic factor, recombinant, single chain)	Individual with factor VIII deficiency (hemophilia A) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
Alphanate (factor VIII - antihemophilic factor/von Willebrand factor complex)	**EITHER** of the following: • Treatment and prevention of bleeding in hemophilia A • Von Willebrand disease (VWD) when there is a failure, contraindication or intolerance to desmopressin, and the indication is for surgical and/or invasive procedures. NOT indicated for severe VWD (type 3) undergoing major surgery
Alphanine SD (factor IX, human plasma-derived)	Individual with factor IX deficiency (hemophilia B) for prevention or control of bleeding.
Alprolix (factor IX, recombinant, Fc fusion protein)	Individual with factor IX deficiency (hemophilia B) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
ATryn [antithrombin III (recombinant)]	Prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient individuals
BeneFIX (factor IX, recombinant)	Individual with factor IX deficiency (hemophilia B) for **EITHER** of the following: • Prevention or control of bleeding • Peri-operative management of bleeding
Coagadex (coagulation Factor X [human])	Individual with coagulation factor X deficiency with **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding in individuals with mild or moderate hereditary factor X deficiency

Product	Criteria for Use
	• Routine prophylaxis to reduce the frequency of bleeding episodes
Corifact [factor XIII Concentrate (human plasma-derived)]	Individual with factor XIII deficiency for **EITHER** of the following: • Routine prophylactic treatment • Peri-operative management of bleeding
Eloctate (antihemophilic factor [recombinant, Fc fusion protein])	Individual with factor VIII deficiency (hemophilia A) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
Esperoct (antihemophilic factor [recombinant] glycoPEGylated-exei)	Individual with factor VIII deficiency (hemophilia A) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
FEIBA (anti-inhibitor coagulant complex)	**EITHER** of the following: • Treatment of an individual with either congenital hemophilia A or B, with inhibitors for **ANY** of the following: o On-demand treatment and control of bleeding episodes o Peri-operative management of bleeding o Routine prophylaxis to reduce the frequency of bleeding episodes • Treatment of spontaneous bleeding episodes or to cover surgical interventions in an individual with acquired inhibitor titer to Factor VIII greater than 5 Bethesda units, or inhibitors to factors XI or XII.
Fibryga (fibrinogen concentrate)	Treatment of acute bleeding episodes in an individual with congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia) and **ALL** of the following: • Individual 13 years of age or older • Diagnosis confirmed by **BOTH** of the following: o Prolonged activated partial thromboplastin time and prothrombin time at baseline, as defined by the laboratory reference values; AND o Lower than normal plasma functional and antigenic fibrinogen levels at baseline, as defined by the laboratory reference values
Hemlibra (emicizumab-kxwh)	**BOTH** of the following: • Diagnosis of hemophilia A (congenital factor VIII deficiency) and documentation of **ANY** of the following: o Factor VIII inhibitors o Severe hemophilia defined as pre-treatment factor VIII level less than 1% o Mild or moderate hemophilia (defined as factor VIII level of 1% to less than 40%) and ANY of the following: ▪ 1 or more episodes of bleeding into the central nervous system or other serious, life-threatening bleed ▪ 1 or more episodes of bleeding into large joint (ankles, knees, hips, elbows, shoulders) and age 3 years or younger ▪ 2 or more episodes of bleeding into large joints (ankles, knees, hips, elbows, shoulders) ▪ Presence of joint disease documented by physical examination and plain radiographs of the affected joints • Use is for routine prophylaxis to prevent or reduce the frequency of bleeding episodes When criteria are met, Hemlibra will be approved for a loading dose of 3 mg/kg once weekly for 4 weeks, followed by any of the 3 maintenance dosing regimens: • 1.5 mg/kg once weekly • 3 mg/kg every 2 weeks • 6 mg/kg every 4 weeks
Hemofil M	Individual with factor VIII deficiency (hemophilia A) for **ANY** of the following:

Product	Criteria for Use
(factor VIII, human plasma-derived)	• On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
Humate-P (factor VIII - antihemophilic factor/von Willebrand factor complex)	**EITHER** of the following: • Treatment and prevention of bleeding in hemophilia A in an adult • Mild to moderate VWD when there is failure, contraindication or intolerance to desmopressin OR severe VWD for EITHER of the following indications: o Treatment of spontaneous and/or trauma-induced bleeding episodes o Prevention of excessive bleeding during and/or following surgery
Idelvion (factor IX, recombinant, albumin fusion protein)	Individual with factor IX deficiency (hemophilia B) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
Ixinity (factor IX, recombinant)	Individual with factor IX deficiency (hemophilia B) for **EITHER** of the following: • Prevention or control of bleeding • Peri-operative management of bleeding
Jivi (antihemophilic factor (recombinant)	Previously treated individual 12 years of age and older with factor VIII deficiency (hemophilia A) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
Koate (factor VIII, human plasma-derived)	Individual with factor VIII deficiency (hemophilia A) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
Kogenate FS (factor VIII, recombinant)	Individual with factor VIII deficiency (hemophilia A) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
Kovaltry (factor VIII, recombinant)	Individual with factor VIII deficiency (hemophilia A) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
Mononine (factor IX, human plasma-derived)	Individual with factor IX deficiency (hemophilia B) for prevention or control of bleeding.
Novoeight (factor VIII, recombinant)	Individual with factor VIII deficiency (hemophilia A) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
NovoSeven RT (factor VIIa)	**EITHER** of the following: • Treatment of bleeding episodes and peri-operative management in an individual with **ANY** of the following: o Hemophilia A or B with inhibitors o Congenital Factor VII (FVII) deficiency o Glanzmann's thrombasthenia with refractoriness to platelet transfusions • Treatment of bleeding episodes and peri-operative management in an adult with acquired hemophilia
Nuwiq (factor VIII, recombinant)	Individual with factor VIII deficiency (hemophilia A) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding

Product	Criteria for Use
	• Routine prophylaxis to reduce the frequency of bleeding episodes
Obizur [antihemophilic factor (recombinant, porcine sequence)]	Treatment for bleeding episodes in an adult when **BOTH** of the following are met: • Diagnosis of acquired hemophilia A that is confirmed by documentation of autoimmune inhibitory antibodies to human factor VIII • Individual does NOT have congenital hemophilia A or von Willebrand disease
Profilnine [factor IX, complex (human plasma-derived)]	Individual with factor II, IX (hemophilia B), or X deficiency for prevention or control of bleeding.
Rebinyn (factor IX, recombinant, glycoPEGylated)	Individual with factor IX deficiency (hemophilia B) for **EITHER** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding
Recombinate (factor VIII, recombinant)	Individual with factor VIII deficiency (hemophilia A) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
RiaSTAP (fibrinogen concentrate)	Treatment of acute bleeding episodes in an individual with congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia) and **ALL** of the following: • Individual 13 years of age or older • Diagnosis confirmed by **BOTH** of the following: o Prolonged activated partial thromboplastin time and prothrombin time at baseline, as defined by the laboratory reference values; AND o Lower than normal plasma functional and antigenic fibrinogen levels at baseline, as defined by the laboratory reference values
Rixubis (factor IX, recombinant)	Individual with factor IX deficiency (hemophilia B) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
Thrombate III [antithrombin III (human)]	Treatment of an individual with hereditary antithrombin III deficiency for **EITHER** of the following: • Treatment and prevention of thromboembolism • Prevention of peri-operative and peri-partum thromboembolism
Tretten [factor XIII A-Subunit (recombinant)]	Routine prophylaxis of bleeding in an individual with congenital factor XIII A-subunit deficiency.
Vonvendi (von Willebrand factor, recombinant)	Individual 18 years of age or older diagnosed with von Willebrand disease meeting **EITHER** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding
Wilate (von Willebrand factor/coagulation factor VIII complex)	On-demand treatment and control of bleeding episodes or peri-operative management of bleeding in an individual with severe von Willebrand disease (VWD) or an individual with mild or moderate VWD when there is documented failure/inadequate response, contraindication per FDA label, or intolerance to desmopressin.
Xyntha (factor VIII, recombinant)	Individual with factor VIII deficiency (hemophilia A) for **ANY** of the following: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes

Clotting Factor products are considered experimental, investigational, or unproven for any other use.

Clotting Factors products are considered medically necessary for continued use when the individual continues to meet the initial criteria.

Initial and reauthorization is up to 12 months unless otherwise stated.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Clotting Factors or Antithrombin.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

General Background

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative:
No recommendations are available for prophylaxis or treatment of congenital bleeding disorders.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)
Anti-inhibitor coagulant complex, AICC, is a drug used to treat hemophilia in patients with factor VIII inhibitor antibodies. AICC has been shown to be safe and effective and has Medicare coverage when furnished to patients with hemophilia A and inhibitor antibodies to factor VIII who have major bleeding episodes and who fail to respond to other, less expensive therapies.

Hemophilia A

Hemophilia A or classic hemophilia is a deficiency of factor VIII. Factor VIII, or antihemophilic factor, is an endogenous glycoprotein necessary for blood clotting and hemostasis. It is a cofactor necessary for factor IX to activate factor X in the intrinsic pathway. Per the National Hemophilia Foundation (NHF), hemophilia occurs in 1 in 5,000 live births in the United States and hemophilia A is 4 times more common than hemophilia B. (NHF, 2016) The average normal plasma activity of factor VIII is designated as 100%, and a factor VIII concentration of 25% of normal is required for hemostasis. Patients with severe hemophilia have a factor VIII concentration of less than 1% of normal and frequently experience bleeding even in the absence of trauma. Patients with a factor VIII concentration between 1% and 5% (moderate hemophilia) experience less bleeding, and patients with a factor VIII concentration greater than 5% (mild hemophilia) usually experience bleeding only after obvious trauma. The administration of factor VIII temporarily replaces the missing clotting factor to correct or prevent bleeding episodes.

Factor VIII is obtained from pooled human plasma or produced by recombinant deoxyribonucleic acid (DNA) technology. Three products contain factor VIII and von Willebrand factor (Alphanate, Humate-P, and Koate), but only Alphanate and Humate-P have the indication for the treatment of von Willebrand disease. Hemlibra 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.

FDA Approved Products for Hemophilia A

Brand Name	Approved Indication(s)
Advate (antihemophilic factor, recombinant)	Advate [Antihemophilic Factor (Recombinant)] is a recombinant antihemophilic factor indicated for use in children and adults with hemophilia A (congenital factor VIII deficiency) for: • Control and prevention of bleeding episodes. • Peri-operative management. • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes. Advate is not indicated for the treatment of von Willebrand disease.

Brand Name	Approved Indication(s)
Adynovate (antihemophilic factor [recombinant], pegylated)	Adynovate, Antihemophilic Factor (Recombinant), PEGylated, is a human antihemophilic factor indicated in children and adults with hemophilia A (congenital factor VIII deficiency) for: • On-demand treatment and control of bleeding episodes • Peri-operative management • Routine prophylaxis to reduce the frequency of bleeding episodes Limitation of Use: Adynovate is not indicated for the treatment of von Willebrand disease.
Afstyla (antihemophilic factor [recombinant], single chain)	Afstyla, Antihemophilic Factor (Recombinant), Single Chain is a recombinant, antihemophilic factor indicated in adults and children with hemophilia A (congenital Factor VIII deficiency) for: • On-demand treatment and control of bleeding episodes, • Routine prophylaxis to reduce the frequency of bleeding episodes, • Peri-operative management of bleeding. Limitations of Use: Afstyla is not indicated for the treatment of von Willebrand disease.
Alphanate (antihemophilic factor/von Willebrand factor complex [human])	Alphanate, (antihemophilic factor/von Willebrand factor complex [human]), is indicated for: • Control and prevention of bleeding episodes and peri-operative management in adult and pediatric patients with Factor VIII (FVIII) deficiency due to hemophilia A. • Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease (VWD) in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.
Eloctate (antihemophilic factor [recombinant, Fc fusion protein])	Eloctate, Antihemophilic Factor (Recombinant), Fc Fusion Protein, is a recombinant DNA derived, antihemophilic factor indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for: • On-demand treatment and control of bleeding episodes, • Peri-operative management of bleeding, • Routine prophylaxis to reduce the frequency of bleeding episodes. Limitation of Use: Eloctate is not indicated for the treatment of von Willebrand disease.
Esperoct (antihemophilic factor [recombinant] glycoPEGylated-exei)	Esperoct [antihemophilic factor (recombinant), glycoPEGylated-exei] is a recombinant DNA-derived coagulation Factor VIII concentrate indicated for use in adults and children with hemophilia A for: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes Limitation of Use: Esperoct is not indicated for the treatment of von Willebrand disease.
Hemlibra (emicizumab-kxwh)	Hemlibra 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])	Hemofil M is indicated in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes. Hemofil M is not indicated in von Willebrand's disease.
Humate-P (antihemophilic factor/von	**Hemophilia A**

Brand Name	Approved Indication(s)
Willebrand factor complex [human])	Humate-P, Antihemophilic Factor/von Willebrand Factor Complex (Human), is indicated for treatment and prevention of bleeding in adults with hemophilia A (classical hemophilia). **Von Willebrand Disease (VWD)** Humate-P is also indicated in adult and pediatric patients with von Willebrand disease (VWD) for: • Treatment of spontaneous and trauma-induced bleeding episodes, and • Prevention of excessive bleeding during and after surgery. This applies to patients with severe VWD as well as patients with mild to moderate VWD where use of desmopressin (DDAVP) is known or suspected to be inadequate. Controlled clinical trials to evaluate the safety and efficacy of prophylactic dosing with Humate-P to prevent spontaneous bleeding have not been conducted in VWD subjects.
Jivi (antihemophilic factor (recombinant)	Jivi, antihemophilic factor (recombinant), PEGylated-aucl, is a recombinant DNA-derived, Factor VIII concentrate indicated 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 • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes <u>Limitations of Use:</u> Jivi is not indicated for use in children < 12 years of age due to greater risk for hypersensitivity reactions. Jivi is not indicated for use in previously untreated patients (PUPs). Jivi is not indicated for the treatment of von Willebrand disease.
Koate (antihemophilic factor [human])	Koate is a human plasma-derived antihemophilic factor indicated for the control and prevention of bleeding episodes or in order to perform emergency and elective surgery in patients with hemophilia A (hereditary Factor VIII deficiency). <u>Limitation of Use:</u> Koate is not indicated for the treatment of von Willebrand disease.
Kogenate FS (antihemophilic factor [recombinant])	Kogenate FS is a recombinant antihemophilic factor indicated for: • On-demand treatment and control of bleeding episodes in adults and children with hemophilia A. • Peri-operative management of bleeding in adults and children with hemophilia A. • Routine prophylaxis to 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. • Routine prophylaxis to 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])	Kovaltry, Antihemophilic Factor (Recombinant), is a recombinant, human DNA sequence derived, full length Factor VIII concentrate indicated for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes Kovaltry is not indicated for the treatment of von Willebrand disease.

Brand Name	Approved Indication(s)
Novoeight (antihemophilic factor [recombinant])	Novoeight, Antihemophilic Factor (Recombinant), is a human antihemophilic factor (human blood coagulation factor VIII (FVIII)) indicated for use in adults and children with hemophilia A for: • On-demand treatment and control of bleeding episodes • Peri-operative management • Routine prophylaxis to reduce the frequency of bleeding episodes Novoeight is not indicated for the treatment of von Willebrand disease.
Nuwiq (antihemophilic factor [recombinant])	Nuwiq is a recombinant antihemophilic factor [blood coagulation factor VIII (Factor VIII)] indicated in adults and children with Hemophilia A for: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes Nuwiq is not indicated for the treatment of von Willebrand Disease.
Obizur (antihemophilic factor [recombinant, porcine sequence])	Obizur, Antihemophilic Factor (Recombinant), Porcine Sequence, is a recombinant DNA derived, antihemophilic factor indicated for the treatment of bleeding episodes in adults with acquired hemophilia A. Limitations of Use: • Safety and efficacy of Obizur has not been established in patients with baseline anti-porcine factor VIII inhibitor titer greater than 20 BU. • Obizur is not indicated for the treatment of congenital hemophilia A or von Willebrand disease.
Recombinate (antihemophilic factor [recombinant])	The use of Recombinate [Antihemophilic Factor (Recombinant)] is indicated in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes. Recombinate is also indicated in the peri-operative management of patients with hemophilia A (classical hemophilia). Recombinate can be of therapeutic value in patients with acquired Factor VIII inhibitors not exceeding 10 Bethesda Units per mL. In clinical studies with Recombinate, patients with inhibitors who were entered into the previously treated patient trial and those previously untreated children who have developed inhibitor activity on study, showed clinical hemostatic response when the titer of inhibitor was less than 10 Bethesda Units per mL. However, in such uses, the dosage of Recombinate should be controlled by frequent laboratory determinations of circulating Factor VIII levels as well as the clinical status of the patient. Recombinate is not indicated in von Willebrand's disease.
Xyntha, (antihemophilic factor [recombinant])	Xyntha, Antihemophilic Factor (Recombinant), is indicated for use in adults and children with hemophilia A (congenital factor VIII deficiency) for: • On-demand treatment and control of bleeding episodes • Peri-operative management Xyntha does not contain von Willebrand factor, and therefore is not indicated in patients with von Willebrand's disease.

Professional Societies/Organizations for Management of Hemophilia A
The National Hemophilia Foundation (NHF) Medical and Scientific Advisory Council (MASAC) has recommendations concerning products used for the treatment of hemophilia and other bleeding disorders. It is noted that recombinant Factor VIII products are the recommended treatment of choice for patients with hemophilia A. The MASAC recommendations regarding plasma-derived Factor VIII products state that improved viral-depleting processes and donor screening practices have greatly reduced the risk of transmission and human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C virus (HCV). (MASAC, 2018)

Hemophilia B

Hemophilia B or Christmas disease is a deficiency of factor IX. Factor IX is activated by factor VIIa or factor XIa. Activated factor IX, along with factor VIII, will activate factor X. As with hemophilia A, hemophilia B is classified as mild, moderate, or severe depending on the percentage of normal plasma factor level obtained rather than the severity of bleeding. Per the National Hemophilia Foundation (NHF), hemophilia occurs in 1 in 5,000 live births in the United States and hemophilia A is 4 times more common than hemophilia B. (NHF, 2016)

Factor IX (human) is a highly purified concentrate of factor IX and contains only non-therapeutic concentrations of factors II, VII and X. Therefore, factor IX (human) should not be used for replacement treatment of factor II, VII, or X deficiencies or for the treatment or reversal of coumarin anticoagulant-induced hemorrhage or hemorrhagic states caused by hepatitis-induced lack of production of liver–dependent coagulation factors. Recombinant factor IX is produced using genetically engineered Chinese hamster ovary cell lines.

FDA Approved Products for Hemophilia B

Brand Name	Approved Indication(s)
AlphaNine SD (factor IX [human])	AlphaNine SD is indicated 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 (factor IX [recombinant, Fc fusion protein])	Alprolix, Coagulation Factor IX (Recombinant), Fc Fusion Protein, is a recombinant DNA derived, coagulation Factor IX concentrate indicated in adults and children with hemophilia B (congenital Factor IX deficiency) for: • On demand treatment and control of bleeding episodes • Peri-operative management of bleeding, • Routine prophylaxis to reduce the frequency of bleeding episodes. Limitation of Use: Alprolix is not indicated for induction of immune tolerance in patients with hemophilia B.
BeneFIX (factor IX [recombinant])	BeneFIX, Coagulation Factor IX (Recombinant), is a human blood coagulation factor indicated in adult and pediatric patients with hemophilia B (congenital factor IX deficiency or Christmas disease) for: • control and prevention of bleeding episodes • Peri-operative management Limitations of Use: BeneFIX is NOT indicated for: • Treatment of other factor deficiencies (e.g., factors II, VII, VIII, and X) • Treatment of hemophilia A patients with inhibitors to factor VIII • Reversal of coumarin-induced anticoagulation • Treatment of bleeding due to low levels of liver-dependent coagulation factors
Idelvion (Coagulation Factor IX [recombinant], Albumin Fusion Protein)	Idelvion, Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP), a recombinant DNA-derived coagulation Factor IX concentrate, is indicated in children and adults with Hemophilia B (congenital Factor IX deficiency) for: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes Limitations of Use: Idelvion is not indicated for immune tolerance induction in patients with Hemophilia B.
Ixinity	Ixinity, Coagulation Factor IX (Recombinant), is a human blood coagulation factor indicated in adults and children ≥ 12 years of age with hemophilia B for:

Brand Name	Approved Indication(s)
(factor IX [recombinant])	• Control and prevention of bleeding episodes • Peri-operative management Ixinity is not indicated for induction of immune tolerance in patients with hemophilia B.
Mononine (factor IX [human])	Mononine is indicated for the prevention and control of bleeding in Factor IX deficiency, also known as Hemophilia B or Christmas disease. Limitations of Use: Mononine is not indicated in the treatment or prophylaxis of Hemophilia A patients with inhibitors to Factor VIII. Mononine contains non-detectable levels of Factors II, VII and X (<0.0025 IU per Factor IX unit using standard coagulation assays) and is, therefore, not indicated for replacement therapy of these clotting factors. Mononine 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.
Profilnine (factor IX complex [human])	Profilnine, Factor IX Complex, is indicated for the prevention and control of bleeding in patients with factor IX deficiency (hemophilia B). Profilnine contains non-therapeutic levels of factor VII, and is not indicated for use in the treatment of factor VII deficiency.
Rebinyn (factor IX, recombinant, glycoPEGylated)	Rebinyn, Coagulation Factor IX (Recombinant), GlycoPEGylated, is a recombinant DNA-derived coagulation Factor IX concentrate indicated for use in adults and children with hemophilia B for: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding Limitations of Use: Rebinyn is not indicated for routine prophylaxis in the treatment of patients with hemophilia B. Rebinyn is not indicated for immune tolerance induction in patients with hemophilia B.
Rixubis (factor IX [recombinant])	Rixubis (Coagulation Factor IX [Recombinant]) is an antihemophilic factor indicated in adults and children with hemophilia B for: • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes. Rixubis is not indicated for induction of immune tolerance in patients with hemophilia B.

Professional Societies/Organizations for Management of Hemophilia B
In April 2018, the Medical and Scientific Council (MASAC) from the National Hemophilia Foundation (NHF) updated recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. The guidelines discuss Factor IX products. Due to safety issues, recombinant Factor IX is the treatment of choice for patients in the management of hemophilia B. Regarding plasma-derived Factor IX concentrates, improved viral-depleting processes and donor screening practices have led to plasma-derived Factor IX products that have a greatly reduced risk for transmission of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Due to higher purity and only limited amounts of other factors contained in the products, AlphaNine SD and Mononine are the human plasma-derived products that are considered to be of high purity and are recognized options by MASAC in the management of hemophilia B. Profilnine is used in patients with Factor II and/or X deficiency. (MASAC, 2018)

Hemophilia A or B with Inhibitors

Approximately 15-20% of people with hemophilia will develop inhibitors (antibodies) to the product that they use for prevention and treatment of bleeding. (CDC, 2016) Two products are FDA approved for hemophilia A and B patients with inhibitors.

FDA Approved Products for Hemophilia A and B with Inhibitors

Brand Name	Approved Indication(s)
FEIBA	FEIBA is an Anti-Inhibitor Coagulant Complex indicated for use in hemophilia A and B patients with inhibitors for: • Control and prevention of bleeding episodes • Peri-operative management • 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 coagulation factor VIII or coagulation factor IX.
Hemlibra (emicizumab-kxwh)	Hemlibra 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.
NovoSeven RT (coagulation factor VIIa [recombinant])	NovoSeven RT (Coagulation Factor VIIa [Recombinant]) is a coagulation factor indicated for: • Treatment of bleeding episodes and peri-operative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets • Treatment of bleeding episodes and peri-operative management in adults with acquired hemophilia

FEIBA, Anti-Inhibitor Coagulant Complex is a freeze-dried sterile human plasma fraction with Factor VIII inhibitor bypassing activity. FEIBA contains Factors II, IX, and X, mainly non-activated, and Factor VII mainly in the activated form. The product contains approximately equal unitages of Factor VIII inhibitor bypassing activity and Prothrombin Complex Factors.

The use of FEIBA Immuno (AICC) has been described in non-hemophiliacs with acquired inhibitors to Factors VIII, XI, and XII and is listed as a use in the American Hospital Formulary Service (AHFS). (McEvoy, 2015) One case has been reported where FEIBA Immuno (AICC) was effective in a patient with von Willebrand's disease with an inhibitor. Clinical experience suggests that patients with a Factor VIII inhibitor titer of less than 5 B.U. may be successfully treated with Antihemophilic Factor. Patients with titers ranging between 5 and 10 B.U. may either be treated with Antihemophilic Factor or FEIBA (AICC). Cases with Factor VIII inhibitor titers greater than 10 B.U. have generally been refractory to treatment with Antihemophilic Factor.

Hemlibra 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.

Recombinant factor VIIa is another therapeutic option that can be used for the prevention and control of bleeding in hemophilia patients with inhibitors. The treatment of choice depends on several factors including the severity and location of the bleed, level and type of inhibitors, and whether the patient has a history of an anamnestic increase in inhibitor levels following use of preparations containing Factor VIII or Factor IX.

Professional Societies/Organizations for Management of Hemophilia A and B with Inhibitors

The National Hemophilia Foundation (NHF) Medical and Scientific Advisory Council (MASAC) has recommendations concerning products used for the treatment of hemophilia, as well as guidelines specific to treatment of hemophilia patients with inhibitors (2018 and 2013, respectively). (MASAC 2018; MASAC 2013)

FEIBA is supported in these guidelines and noted to be indicated for use in hemophilia patients only when an inhibitor is present.

von Willebrand Disease

Von Willebrand factor (VWF) promotes platelet aggregation and platelet adhesion on damaged vascular endothelium and serves as a stabilizing carrier protein for the pro-coagulant protein, Factor VIII. Von Willebrand disease, a deficiency of VWF or having abnormal VWF, is a genetic disorder that affects up to 1% of the population. (NHF, 2016) Treatment options depend on the severity of disease. Von Willebrand disease is generally classified as one of 3 types: Type 1 is the most common and mildest form. Type 2 is when VWF is abnormal and is further subdivided into four subtypes: 2A, 2B, 2M, or 2N. Type 3 is a complete absence of VWF and is the most severe.

FDA Approved Products for von Willebrand Disease

Brand Name	Approved Indication(s)
Alphanate (antihemophilic factor/von Willebrand factor complex [human])	Alphanate, (antihemophilic factor/von Willebrand factor complex [human]), is indicated for: • Control and prevention of bleeding episodes and peri-operative management in adult and pediatric patients with Factor VIII (FVIII) deficiency due to hemophilia A. • Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease (VWD) in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.
Humate-P (antihemophilic factor/von Willebrand factor complex [human])	**Hemophilia A** Humate-P, Antihemophilic Factor/von Willebrand Factor Complex (Human), is indicated for treatment and prevention of bleeding in adults with hemophilia A (classical hemophilia). **Von Willebrand Disease (VWD)** Humate-P is also indicated in adult and pediatric patients with von Willebrand disease (VWD) for: 1) Treatment of spontaneous and trauma-induced bleeding episodes, and 2) Prevention of excessive bleeding during and after surgery. This applies to patients with severe VWD as well as patients with mild to moderate VWD where use of desmopressin (DDAVP) is known or suspected to be inadequate. Controlled clinical trials to evaluate the safety and efficacy of prophylactic dosing with Humate-P to prevent spontaneous bleeding have not been conducted in VWD subjects.
Vonvendi (von Willebrand factor [recombinant])	Vonvendi [von Willebrand factor (recombinant)] is a recombinant von Willebrand factor (rVWF) indicated for use in adults (age 18 and older) diagnosed with von Willebrand disease (VWD) for: • On-demand treatment and control of bleeding episodes. • Peri-operative management of bleeding.
Wilate (von Willebrand factor/coagulation factor VIII complex [human])	Wilate is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD) as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated. Clinical trials to evaluate the safety and efficacy of prophylactic dosing with Wilate to prevent spontaneous bleeding have not been conducted in VWD subjects. Wilate is not indicated for the prevention of excessive bleeding during and after surgery in VWD patients. Wilate is not indicated for Hemophilia A.

Professional Societies/Organizations for Management of von Willebrand Disease

In 2012 the American Society of Hematology (ASH) published a summary guide to the National Heart, Lung, and Blood Institute 2007 recommendations for managing von Willebrand disease. Desmopressin (DDAVP) and von

Willebrand factor replacement products (Humate-P, Wilate, Koate, and Alphanate) are listed as therapies to elevate VWF. Some of the key management recommendations from the guide regarding treatment of minor and major bleeding and prophylaxis for minor and major surgery include:

- Minor bleeding should be treated with intravenous or nasal DDAVP, if supported by results of a DDAVP trial.
- If response to DDAVP is inadequate, VWF concentrate should be used, with dosing primarily based on VWF:RCo units and secondarily on FVIII units.
- For minor surgery, prophylaxis should achieve VWF:RCo and FVIII activity levels >/= 30 IU/dL, and preferably > 50 IU/dL, for 1-5 days.
- For severe bleeding (e.g. intracranial, retroperitoneal) or prophylaxis of major surgery, 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. (ASH, 2012)

The Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) includes recommendations for management of VWD. Most patients with von Willebrand Disease type 1 may be treated with either desmopressin (either parenterally [DDAVP injection] or by a highly concentrated nasal spray [Stimate nasal spray]). For surgery, trauma, or other serious bleeding episodes, if hemostasis is not achieved using DDAVP, a Factor VIII concentrate that contains high molecular weight multimers of vWF should be used. Patients with type 2B and type 3 von Willebrand Disease, and those with type 1, 2A, 2M, and 2N who have not responded adequately to DDAVP should be treated with a Factor VIII concentrate that contains higher molecular weight multimers of vWF. Products FDA-approved for this use include Alphanate, Humate P, and Wilate. Koate may be effective but it not FDA-approved for this use. (MASAC, 2018)

Desmopressin (DDAVP) is recommended for the majority of type 1 patients and for clinically responsive type 2A patients. VWF-containing Factor VIII concentrates are recommended for type 1 and 2A patients who become transiently unresponsive to DDAVP and in surgical situations and for type 2B and 3 VWD that do not respond to DDAVP. While not FDA-approved for VWD, Koate- is listed as possibly effective for some patients. (NHF, 2015)

Factor VII Deficiency

Recombinant coagulation Factor VIIa (NovoSeven RT) is a vitamin K-dependent glycoprotein that is structurally similar to human plasma-derived Factor VIIa. It promotes hemostasis by activating the extrinsic pathway of the coagulation cascade. When complexed with tissue factor, it can activate coagulation Factor X to Factor Xa, and Factor IX to Factor IXa. Activated Factor X (Factor Xa), complexed with other factors converts prothrombin to thrombin and fibrinogen to fibrin to form a hemostatic plug, inducing local hemostasis. The incidence of factor VII deficiency is estimated as 1 per 300,000-500,000. (NHF, 2016)

FDA Approved Product for Factor VII Deficiency

Brand Name	Approved Indication(s)
NovoSeven RT (coagulation factor VIIa [recombinant])	NovoSeven RT (Coagulation Factor VIIa [Recombinant]) is a coagulation factor indicated for: • Treatment of bleeding episodes and peri-operative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets • Treatment of bleeding episodes and peri-operative management in adults with acquired hemophilia

Professional Societies/Organizations for Management of Factor VII Deficiency

The National Hemophilia Foundation (NHF) Medical and Scientific Advisory Council (MASAC) has recommendations concerning products used for the treatment of hemophilia and other bleeding disorders. NovoSeven RT is supported as a treatment option for inherited hemophilia A or B with inhibitors, acquired hemophilia A, and Factor VII deficiency (Glanzmann's thrombasthenia is not addressed in the guidelines). (MASAC, 2018) MASAC recommendations (2013) also state that NovoSeven RT and FEIBA have demonstrated efficacy and safety for prophylactic use for patients with inhibitors in hemophilia A and hemophilia B. (MASAC, 2013)

Factor XIII Deficiency

Factor XIII is a plasma glycoprotein responsible for normal clot formation. Activated Factor XIII catalyzes fibrin cross-linking, the final step in the coagulation cascade. At steady state, Factor XIII concentrate has a half-life of approximately 6 days. Congenital factor XIII deficiency is very rare with an incidence of one person every 5 million births. (NHF, 2016)

FDA Approved Product for Factor XIII Deficiency

Brand Name	Approved Indication(s)
Corifact (factor XIII concentrate [human])	Corifact is a Factor XIII Concentrate indicated for routine prophylactic treatment and peri-operative management of surgical bleeding in adult and pediatric patients with congenital FXIII deficiency.
Tretten (coagulation factor XIII A-subunit [recombinant])	Tretten, Coagulation Factor XIII A-Subunit (Recombinant), is indicated for routine prophylaxis for bleeding in patients with congenital factor XIII A-subunit deficiency. Tretten is not for use in patients with congenital factor XIII B-subunit deficiency

Professional Societies/Organizations for Management of Factor XIII Deficiency

The National Hemophilia Foundation Medical and Scientific Advisory Council has guidelines for the treatment of hemophilia and other bleeding disorders. Corifact is recommended in patients who have Factor XIII deficiency. (MASAC, 2018)

The National Hemophilia Foundation Medical and Scientific Advisory Council has guidelines for the treatment of hemophilia and other bleeding disorders (revised April 2018). Tretten is recommended in patients who have factor XIII deficiency who lack the factor XIII-A subunit. It will not work in patients who only lack factor XIII-B subunit. (MASAC, 2018)

Factor X Deficiency

Factor X is needed for effective hemostasis. Factor X is an inactive zymogen, which can be activated by Factor IXa (via the intrinsic pathway) or by Factor VIIa (via the extrinsic pathway). Factor X is converted from its inactive form to the active form (Factor Xa) by the cleavage of a 52-residue peptide from the heavy chain. Factor Xa associates with Factor Va on a phospholipid surface to form the prothrombinase complex, which activates prothrombin to thrombin in the presence of calcium ions. Thrombin then acts upon soluble fibrinogen and Factor XIII to generate a cross-linked fibrin clot. The National Hemophilia Foundation estimates the incidence at 1 in 500,000 to 1 in a million. (NHF, 2016)

FDA Approved Product for Factor X Deficiency

Brand Name	Approved Indication(s)
Coagadex (coagulation factor X [human])	Coagadex, Coagulation Factor X (Human), is a plasma-derived human blood coagulation Factor indicated in adults and children with hereditary Factor X deficiency for: • Routine prophylaxis to reduce the frequency of bleeding episodes • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding in patients with mild and moderate hereditary Factor X deficiency <u>Limitation of Use</u>: Peri-operative management of bleeding in major surgery in patients with severe hereditary Factor X deficiency has not been studied.

Professional Societies/Organizations for Management of Factor X deficiency

The National Hemophilia Foundation Medical and Scientific Advisory Council has guidelines for the treatment of hemophilia and other bleeding disorders (revised April 2018). Coagadex is recommended in patients who have Factor X deficiency. (MASAC, 2018)

Fibrinogen Deficiency

Fibrinogen deficiency, or factor I deficiency, affects men and women and is further classified as either a quantitative or qualitative disorder. Afibrinogenemia (no production of fibrinogen) and hypofibrinogenemia (insufficient production of normal structure fibrinogen to allow for hemostasis) are quantitative disorders. Dysfibrinogenemia is a qualitative disorder, meaning there is adequate production of fibrinogen that does not function or clot properly. (NHF, 2016)

FDA Approved Products for Fibrinogen Deficiency

Brand Name	Approved Indication(s)
Fibryga (fibrinogen concentrate [human])	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.
RiaSTAP (fibrinogen concentrate [human])	RiaSTAP, Fibrinogen Concentrate (Human) is a human blood coagulation factor indicated for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

Antithrombin Deficiency

Antithrombin (AT) is a natural anticoagulant that inhibits thrombin, factor Xa, and other enzymes. AT deficiency can be either inherited or acquired. Congenital AT deficiency is an autosomal dominant trait with an incidence of 1:2,000 to 1:5,000. Type 1 AT deficiency is a quantitative reduction in AT and Type II is a qualitative impairment. Normal plasma AT activity is 80-120% and 40-50% activity is considered a clinically important deficiency. (Pal, 2010)

Exogenous AT-III (human) is derived from pooled human plasma and must be administered intravenously. Antithrombin III clotting factor complexes are rapidly removed from the circulation by binding to a specific receptor present on hepatocytes. The elimination half-life of AT-III (human) is approximately two to three days. However, the half-life may be decreased following surgery, hemorrhage or acute thrombosis, and during concurrent use of heparin. Recombinant antithrombin is produced through genetically engineered goat milk. Recombinant antithrombin has a shorter half-life and is cleared more rapidly compared to human plasma-derived antithrombin.

FDA Approved Products for Antithrombin Deficiency

Brand Name	Approved Indication(s)
ATryn (antithrombin [recombinant])	ATryn is a recombinant antithrombin indicated for the prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients. It is not indicated for treatment of thromboembolic events in hereditary antithrombin deficient patients.
Thrombate III (antithrombin III [human])	Thrombate III is a human antithrombin (AT) indicated in patients with hereditary antithrombin III deficiency for: • Treatment and prevention of thromboembolism • Prevention of peri-operative and peri-partum thromboembolism

Recommended Dosing

FDA Recommended Dosing

- **Advate (antihemophilic factor [recombinant])**

  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous injection after reconstitution only.
  - Each vial of Advate contains the labeled amount of recombinant Factor VIII in International Units (IU).

- Control and prevention of bleeding episodes and peri-operative management:
  - Dose (IU) = body weight (kg) × desired factor VIII rise (IU/dL or % of normal) × 0.5 (IU/kg per IU/dL).
  - Determine treatment frequency based on type of bleeding episode.
- Routine Prophylaxis
  - 20 to 40 IU per kg every other day (3 to 4 times weekly).
  - Alternatively, use every third day dosing regimen targeted to maintain FVIII trough levels ≥ 1%.

➢ **Adynovate (antihemophilic factor [recombinant])**

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For intravenous use after reconstitution only.
- One unit per kilogram body weight will raise the factor VIII level by 2% international units per deciliter (IU per dL). Each vial of ADYNOVATE is labeled with the actual amount of recombinant factor VIII present in IU.
- On-demand treatment and control of bleeding episodes and peri-operative management:
  - Estimated Increment of factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)
  - Dose (IU) = Body Weight (kg) x Desired factor VIII Rise (IU/dL or % of Normal) x 0.5 (IU/kg per IU/dL)
- Routine prophylaxis: Administer 40-50 IU per kg body weight 2 times a week
  (Starting dose of 55 IU per kg body weight 2 times a week patients <12 years of age with a maximum of 70 IU per kg).
- Inject intravenously over a period of less than or equal to 5 minutes (maximum infusion rate of 10 mL per min).

➢ **Afstyla (antihemophilic factor [recombinant], single chain)**

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For intravenous use after reconstitution only.
- Each vial of Afstyla is labeled with the amount of recombinant Factor VIII in international units (IU or unit). One unit per kilogram body weight will raise the Factor VIII level by 2 IU/dL.
- Plasma Factor VIII levels can be monitored using either a chromogenic assay or a one-stage clotting assay – routinely used in US clinical laboratories. **If the one-stage clotting assay is used, multiply the result by a conversion factor of 2 to determine the patient's Factor VIII activity level.**

Calculating Required Dose:
Dose (IU) = Body Weight (kg) x Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

- Routine Prophylaxis:
  - Adults and adolescents (≥12 years): The recommended starting regimen is 20 to 50 IU per kg of Afstyla administered 2 to 3 times weekly.
  - Children (< 12 years): The recommended starting regimen is 30 to 50 IU per kg of Afstyla administered 2 to 3 times weekly. More frequent or higher doses may be required in children < 12 years of age to account for the higher clearance in this age group.
  - The regimen may be adjusted based on patient response.
- Peri-operative Management:
  - Ensure the appropriate Factor VIII activity level is achieved and maintained.

➢ **Alphanate (human antihemophilic factor/von Willebrand factor complex)**

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For Intravenous injection after reconstitution only.

- Alphanate contains the labeled amount of Factor VIII expressed in International Units (IU) FVIII/vial and von Willebrand Factor:Ristocetin Cofactor activity in IU VWF:RCo/vial.
- **Dose:**
  Treatment and Prevention of Bleeding Episodes and Excess Bleeding During and After Surgery in Patients with Hemophilia A
    - Dose (units) = body weight (kg) x desired FVIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).
    - Dosing frequency determined by the type of bleeding episode and the recommendation of the treating physician.

  Treatment and Prevention of Excess Bleeding During and After Surgery or Other Invasive Procedures in Patients with von Willebrand Disease
    - Adults: Pre-operative dose of 60 IU VWF:RCo/kg body weight; subsequent doses of 40-60 IU VWF:RCo/kg body weight.
    - Pediatric: Pre-operative dose of 75 IU VWF:RCo/kg body weight; subsequent doses of 50-75 IU VWF:RCo/kg body weight.

➢ **AlphaNine SD (coagulation factor IX [human]**

- For adult usage:
    - AlphaNine SD should be administered intravenously promptly following reconstitution. Administration of AlphaNine SD within three hours after reconstitution is recommended to avoid the potential ill effect of any inadvertent bacterial contamination occurring during reconstitution. Discard any unused contents into the appropriate safety container.
    - Each vial of AlphaNine SD is labeled with the total units expressed as International Units (IU) of Factor IX, which is referenced to the WHO International Standard. One unit approximates the activity in one mL of pooled normal human plasma.
    - The amount of AlphaNine SD required to establish hemostasis will vary with each patient and depend upon the circumstances. The following formula may be used as a guide in determining the number of units to be administered.
        - Body weight (in kg) x Desired increase in Plasma Factor IX (Percent) x 1.0 IU/kg = Number of Factor IX IU required
        - Example: 70 kg x 40 (% increase) x 1.0 IU/kg = 2,800 IU AlphaNine SD
    - In clinical practice there is variability between patients and their clinical response. Therefore, the Factor IX level of each patient should be monitored frequently during replacement therapy.

- For pediatric usage: See PRECAUTIONS (*Clinical trials for safety and effectiveness in pediatric patients 16 years of age and younger have not been conducted. Across a well-controlled half-life and recovery clinical trial in patients previously treated with Factor IX concentrates of Hemophilia B, the three pediatric patients receiving AlphaNine SD (solvent detergent treated) responded similarly when compared with 15 adult patients. In an ongoing safety and efficacy clinical trial in patients not previously treated with Factor IX concentrates for Hemophilia B, 21 pediatric patients received AlphaNine SD (solvent detergent treated) responded similarly when compared with the five adult patients above the age of 16 years. Adverse events were similar in this group compared to the patients above the age of 16 years. Anecdotal evaluation of the results indicates no safety and efficacy differences between pediatric and adult populations*.)

Treatment Guidelines for Hemorrhagic Events and Surgery in Patients Diagnosed with Hemophilia B

Type of Hemorrhage or Surgical Procedure	Examples	Treatment Guidelines
Minor Hemorrhages	Bruises, cuts or scrapes, uncomplicated joint hemorrhage	FIX levels should be brought to at least 20-30% (20-30 IU FIX/kg/twice daily) until hemorrhage stops and healing has been achieved (1-2 days).

Moderate Hemorrhages	Nose bleeds, mouth and gum bleeds, dental extractions, hematuria	FIX levels should be brought to 25-50% (25-50 IU FIX/kg/twice daily) until healing has been achieved (2-7 days, on average).
Major Hemorrhages	Joint and muscle hemorrhages (especially in the large muscles), major trauma, hematuria, intracranial and intraperitoneal bleeding	FIX levels should be brought to 50% for at least 3-5 days (30-50 IU FIX/kg/twice daily). Following this treatment period, FIX levels should be maintained at 20% (20 IU FIX/kg/twice daily) until healing has been achieved. Major hemorrhages may require treatment for up to 10 days.
Surgery		Prior to surgery, FIX should be brought to 50-100% of normal (50-100 IU FIX/kg/twice daily). For the next 7 to 10 days, or until healing has been achieved, the patient should be maintained at 50-100% FIX levels (50-100 IU FIX/kg/twice daily).

- Dosing requirements and frequency of dosing is calculated on the basis of an initial response of 1% FIX increase achieved per IU of FIX infused per kg body weight and an average half-life for FIX of 18 hours. If dosing studies have revealed that a particular patient exhibits a lower response, the dose should be adjusted accordingly.

- For pediatric usage: See PRECAUTIONS (*Clinical trials for safety and effectiveness in pediatric patients 16 years of age and younger have not been conducted. Across a well-controlled half-life and recovery clinical trial in patients previously treated with Factor IX concentrates of Hemophilia B, the three pediatric patients receiving AlphaNine SD (solvent detergent treated) responded similarly when compared with 15 adult patients. In an ongoing safety and efficacy clinical trial in patients not previously treated with Factor IX concentrates for Hemophilia B, 21 pediatric patients received AlphaNine SD (solvent detergent treated) responded similarly when compared with the five adult patients above the age of 16 years. Adverse events were similar in this group compared to the patients above the age of 16 years. Anecdotal evaluation of the results indicates no safety and efficacy differences between pediatric and adult populations*.)

- **Alprolix (coagulation factor IX [recombinant], Fc fusion protein)**

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For intravenous use after reconstitution only.

On demand treatment and control of bleeding episodes and peri-operative management of bleeding:

- Each vial of Alprolix contains the labeled amount of coagulation Factor IX potency in international units (IU).
- One unit per kilogram body weight of Alprolix increased the circulating Factor IX level by 1% [IU/dL].

Initial Dose: Type of Bleeding	Circulating FIX (IU/dL)	Dosing Interval (hours)
Minor and Moderate	30-60	Repeat every 48 hours as needed
Major	80-100	Consider repeat dose after 6-10 hours, then every 24 hours for 3 days, then every 48 hours until healing achieved

- The maintenance dose or frequency of Alprolix administration is determined by the type of bleeding episode and the recommendation of the treating healthcare provider.

Routine prophylaxis:
50 IU/kg once weekly or 100 IU/kg once every 10 days. Adjust dosing regimen based on individual response.

- **ATryn (recombinant antithrombin)**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous use only after reconstitution.
  - The dosage of ATryn is individualized for each patient. Treatment goal is to restore and maintain functional antithrombin (AT) activity levels between 80% - 120% (0.8 - 1.2 IU/mL) of normal.
  - Administer loading dose as a 15-minute intravenous infusion immediately followed by continuous infusion of the maintenance dose.

	Loading Dose (IU)		Maintenance Dose (IU/hour)	
Surgical Patients	(100 – baseline AT activity) / 2.3	x Body Wt (kg)	(100 – baseline AT activity) / 10.2	x Body Wt (kg)
Pregnant Women	(100 – baseline AT activity) / 1.3	x Body Wt (kg)	(100 – baseline AT activity) / 5.4	x Body Wt (kg)

  - AT activity monitoring is required for proper treatment. Check AT activity once or twice per day with dose adjustments made according to table below.

Initial Monitor Time	AT Level	Dose Adjustment	Recheck AT Level
2 hours after initiation of treatment	< 80%	Increase 30%	2 hours after each dose adjustment
	80% to 120%	None	6 hours after initiation of treatment or dose adjustment
	> 120%	Decrease 30%	2 hours after each dose adjustment

  - Continue administration of ATryn until adequate follow-on anticoagulation has been established.

- **BeneFIX (coagulation factor IX [recombinant])**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For Intravenous use after reconstitution only.
  - One international unit (IU) of BeneFIX per kilogram of body weight increased the circulating activity of factor IX as follows:
    - Adults: 0.8 ± 0.2 IU/dL [range 0.4 to 1.2 IU/dL]
    - Pediatric (< 15 years): 0.7 ± 0.3 IU/dL [range 0.2 to 2.1 IU/dL]
  - Determine the initial estimated dose using the following formula:
    Required units = body weight (kg) x desired factor IX increase (IU/dL or % of normal) x reciprocal of observed recovery (IU/kg per IU/dL)
  - Dosage and duration of treatment with BeneFIX depends on the severity of the factor IX deficiency, the location and extent of bleeding, and the patient's clinical condition, age and recovery of factor IX.

- **Coagadex (coagulation factor X ([human])**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous use only after reconstitution.
  - Each vial of Coagadex contains the labeled amount of Factor X in international units (IU).
  - The dosage and duration of treatment depend on the severity of the Factor X deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

For prophylaxis of bleeding episodes:

Age	Initial Dose	Further Management
Children: Less than 12 years of age	40 IU/kg twice weekly	Monitor trough blood levels of Factor X targeting ≥5 IU/dL and adjust dosage to clinical response and trough levels. Do not exceed a peak level of 120 IU/dL.
Adults and adolescents: 12 years of age or older	25 IU/kg twice weekly	

For treatment of bleeding episodes:

Age	Initial Dose	Further Management
Children: Less than 12 years of age	30 IU/kg	Repeat at intervals of 24 hours until the bleed stops.
Adults and adolescents: 12 years of age or older	25 IU/kg	

For peri-operative management:

Age	Initial Dose	Further Management
Children: Less than 12 years of age	Use a factor of 0.6 to calculate the required dose (see formula in PI).	**Pre-surgery:** raise plasma Factor X levels to 70-90 IU/dL **Post-surgery:** maintain plasma Factor X levels at ≥50 IU/dL until the patient is no longer at risk of bleeding due to surgery
Adults and adolescents: 12 years of age or older	Use a factor of 0.5 to calculate the required dose (see formula in PI).	

- **Corifact (human factor XIII concentrate)**

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For intravenous use only.
- **Dose**
  - 40 International Units (IU) per kg body weight; rate not to exceed 4 mL per min.
  - Adjust dose ±5 IU per kg to maintain 5% to 20% trough level of FXIII activity.

Dose Adjustment Using the Berichrom Activity Assay

FXIII Activity Trough Level (%)	Dosage Change
One trough level of < 5%	Increase by 5 IU per kg
Trough level of 5% to 20%	No change
Two trough levels of > 20%	Decrease by 5 IU per kg
One trough level of > 25%	Decrease by 5 IU per kg

- **Administration**
  - Administer at a rate not exceeding 4 mL per minute
  - For routine prophylaxis, administer every 28 days
  - For peri-operative management of surgical bleeding, individualize dose based on the patient's FXIII activity level, type of surgery, and clinical response
  - Following are dose adjustment examples for peri-operative management in reference to the patient's last prophylactic dose:

Dose Adjustment for Peri-operative Management

Time Since Last Dose	Dose
Within 7 days	Additional dose may not be needed
8-21 days	Additional partial or full dose may be needed based on FXIII activity level
21-28 days	Full prophylactic dose

- **Eloctate (antihemophilic factor [recombinant], Fc fusion protein)**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous use after reconstitution only.
  - Each vial of Eloctate is labeled with the amount of recombinant Factor VIII in international units (IU or unit). One unit per kilogram body weight will raise the Factor VIII level by 2% (IU/dL).
  - For on-demand treatment and control of bleeding episodes and peri-operative management, calculate dose using the following formulas:

    Estimated Increment of Factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)
    OR
    Required Dose (IU) = Body Weight (kg) x Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)
  - For routine prophylaxis: 50 IU/kg every 4 days. Adjust dose based on patient response with dosing in the range of 25-65 IU/kg at 3-5 day intervals.
  - For routine prophylaxis in children less than 6 years of age: 50 IU/kg twice weekly. Adjust dose based on patient response with dosing in the range of 25-65 IU/kg at 3-5 day intervals. More frequent or higher doses up to 80 IU/kg may be required.

- **Esperoct (antihemophilic factor [recombinant], glycoPEGylated-exei)**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*
  - For intravenous infusion after reconstitution only.
  - Each vial label for Esperoct states the actual Factor VIII activity in international units (IU).
  - On-demand treatment/control of bleeding episodes: In adolescents/adults, 40 IU/kg body weight for minor/moderate bleeds and 50 IU/kg body weight for major bleeds; children (<12 years), 65 IU/kg body weight for minor/moderate/major bleeds.
  - Peri-operative management: For minor/major surgery: In adolescents / adults: pre-operative dose of 50 IU/kg body weight; in children (<12 years), pre-operative dose of 65 IU/kg body weight. Frequency of administration is determined by the treating physician.
  - Routine prophylaxis: In adolescents/adults, 50 IU/kg every 4 days; in children (<12 years), 65 IU/kg twice weekly. A regimen may be individually adjusted to less or more frequent dosing based on bleeding episodes.
  - Esperoct also may be dosed to achieve a specific target Factor VIII activity level, depending on the severity of hemophilia, for on-demand treatment/control of bleeding episodes or peri-operative management. To achieve a specific target Factor VIII activity level, use the following formula:
    - Dosage (IU) = Body Weight (kg) x Desired Factor VIII Increase (IU/dL or % normal) x 0.5 (IU/kg per IU/dL).

- **FEIBA (Anti-Inhibitor Coagulant Complex)**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*
  - For intravenous use after reconstitution only.
  - Each vial of FEIBA contains the labeled amount of factor VIII inhibitor bypassing activity in units.

Type of Bleeding	Dose (unit/kg)	Frequency/Duration
Control and Prevention of Bleeding	50 - 100	Determined by the type of bleeding episode
Peri-operative Management	50 - 100	Determined by the type of surgical intervention
Routine Prophylaxis	85	Every other day

- Maximum injection or infusion rate must not exceed 2 units per kg of body weight per minute.

➢ Fibryga (fibrinogen concentrate [human])

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For intravenous use only. Reconstitute prior to use.
- Dose when fibrinogen level is known:
  Dose (mg/kg body weight) =
  [Target fibrinogen level (mg/dL) - measured fibrinogen level (mg/dL)]/1.8 (mg/dL per mg/kg body weight)
- The recommended target fibrinogen plasma level is 100 mg/dL for minor bleeding and 150 mg/dL for major bleeding.
  - Dose when fibrinogen level is unknown: 70 mg/kg body weight.
  - The injection rate should not exceed 5 mL per minute.
  - Monitoring of patient's fibrinogen level is recommended during treatment.

➢ Hemlibra (antihemophilic factor (human), monoclonal modified immunoglobulin G4)

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

Recommended loading dose is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by a maintenance dose of:

- 1.5 mg/kg once every week, or
- 3 mg/kg once every two weeks, or
- 6 mg/kg once every four weeks

➢ Hemofil M (antihemophilic factor (human), method M, monoclonal purified nanofiltered)

- For intravenous use only.
- The expected in vivo peak AHF level, expressed as IU/dL of plasma or % (percent) of normal, can be calculated by multiplying the dose administered per kg body weight (IU/kg) by two. This calculation is based on the clinical finding by Abildgaard, et al which is supported by data from the collaborative study of in vivo recovery and survival with 15 different lots of Hemofil M on 56 hemophiliacs that demonstrated a mean peak recovery point above the mean pre-infusion baseline of about 2.0 IU/dL per infused IU/kg body weight. [Addiego, et al]
- Examples:
  (1) A dose of 1750 IU AHF administered to a 70 kg patient, i.e., 25 IU/kg (1750/70), should be expected to cause a peak post-infusion AHF increase of 25 x 2 = 50 IU/dL (50% of normal).
  (2) A peak level of 70% is required in a 40 kg child. In this situation the dose would be 70/2 x 40 = 1400 IU.
- Recommended Dosage Schedule
  - Physician supervision of the dosage is required. The following dosage schedule may be used as a guide.

HEMORRHAGE		
Degree of hemorrhage	**Required peak post-infusion AHF activity in the blood (as % of normal or IU/dL plasma)**	**Frequency of infusion**
Early hemarthrosis or muscle bleed or oral bleed	20-40	Begin infusion every 12 to 24 hours for one-three days until the bleeding episode as indicated by pain is resolved or healing is achieved.

More extensive hemarthrosis, muscle bleed, or hematoma	30-60	Repeat infusion every 12 to 24 hours for usually three days or more until pain and disability are resolved.
Life threatening bleeds such as head injury, throat bleed, severe abdominal pain	60-100	Repeat infusion every 8 to 24 hours until threat is resolved.
SURGERY		
Type of operation		
Minor surgery, including tooth extraction	60-80	A single infusion plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases.
Major surgery	80-100 (pre- and post-operative)	Repeat infusion every 8 to 24 hours depending on state of healing.

- If bleeding is not controlled with the prescribed dose, determine the plasma level of Factor VIII and administer a sufficient dose of Hemofil M to achieve a satisfactory clinical response.
- Under certain circumstances (e.g., presence of a low titer inhibitor) doses larger than those recommended may be necessary as per standard care. In patients with high titer Factor VIII inhibitors, Hemofil M therapy may not be effective and other therapeutic options should be considered.
- The dosage and duration of treatment depend on the severity of Factor VIII deficiency, the location and extent of the bleeding, and the patient's clinical condition. Careful control of replacement therapy is especially important in cases of major surgery or life threatening hemorrhages.

➢ **Humate-P (human antihemophilic factor/von Willebrand factor complex)**

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- **For intravenous use only.**
- **Hemophilia A**
  - One International Unit (IU) of factor VIII (FVIII) activity per kg body weight increases the circulating FVIII level by approximately 2.0 IU/dL. Individualize dosage based on the patient's weight, type and severity of hemorrhage, FVIII level, and presence of inhibitors.
- **Von Willebrand Disease**
  - Treatment of bleeding episodes – 40-80 IU VWF:Ristocetin Cofactor (RCo) per kg body weight (BW) every 8-12 hours.
  - Prevention of excessive bleeding during and after surgery for all types of VWD.

Type of Surgery (see Table 3 *[of prescribing information*] for complete surgical dosing)	Calculation of Loading Dose Initial maintenance dose should be half the loading dose (see Table 4 *[of prescribing information]* for monitoring recommendations)
Major Surgery	$\frac{\Delta^* \text{ VWF:RCo x BW (kg)}}{\text{IVR}^{\varepsilon}}$ = IU VWF:RCo required
Minor/Oral Surgery±	$\frac{\Delta^* \text{ VWF:RCo x BW (kg)}}{\text{IVR}}$ = IU VWF:RCo required
Emergency Surgery	Administer a dose of 50-60 IU VWF:RCo/kg BW

* Δ = Target peak plasma VWF:RCo level – baseline plasma VWF:RCo level
ε IVR = in vivo recovery as measured in the patient. If the IVR is unknown, use 2.0 IU/dL per IU/kg.
± Oral surgery is defined as extraction of fewer than three teeth, if the teeth are non-molars and have no bony involvement.

- **Idelvion (coagulation factor IX [recombinant] albumin fusion protein)**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous use after reconstitution only.
  - Each vial of Idelvion is labeled with the actual Factor IX potency in international units (IU)
  - One IU of Idelvion per kg body weight is expected to increase the circulating activity of Factor IX as follows:
    - Adolescents and adults: 1.3 IU/dL per IU/kg (2.1)
    - Pediatrics (<12 years): 1 IU/dL per IU/kg
  - Administer intravenously. Do not exceed infusion rate of 10 mL per minute.

  On-demand treatment and control of bleeding episodes and peri-operative management:
  - Dosage and duration of treatment with Idelvion depends on the severity of the Factor IX deficiency, the location and extent of bleeding, and the patient's clinical condition, age and recovery of Factor IX.
  - Determine the initial dose using the following formula:
    Required Dose (IU) = Body Weight (kg) x Desired Factor IX rise (% of normal or IU/dL) x (reciprocal of recovery (IU/kg per IU/dL))
  - Adjust dose based on the patient's clinical condition and response.

  Routine prophylaxis:
  - Patients ≥12 years of age: 25-40 IU/kg body weight every 7 days. Patients who are well-controlled on this regimen may be switched to a 14-day interval at 50-75 IU/kg body weight.
  - Patients < 12 years of age: 40-55 IU/kg body weight every 7 days.

- **Ixinity (coagulation factor IX [recombinant])**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous use after reconstitution only.
  - One international unit (IU) of Ixinity per kg body weight increases the circulating activity of factor IX by 0.98 IU/dL.
  - Initial dose: Required factor IX units (IU) = body weight (kg) x desired factor IX increase (% of normal or IU/dL) x reciprocal of observed recovery (IU/kg per IU/dL).
  - Maintenance dose:
    Depends upon the type of bleed or surgery, clinical response, and the severity of the underlying factor IX deficiency.

- **Jivi (antihemophilic factor (recombinant), PEGylated-aucl)**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous use after reconstitution only.
  - Control of bleeding episodes and peri-operative management
    - Expected recovery: one unit per kilogram body weight of Jivi will increase the Factor VIII level by 2 international units per deciliter (IU/dL). Each vial of Jivi contains the labeled amount of recombinant Factor VIII in IU.
    - Required dose (IU) = body weight (kg) x desired Factor VIII rise (% of normal or IU/dL) x reciprocal of expected recovery (or observed recovery, if available).
    - Estimated Increment of Factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg).
  - Routine prophylaxis
    - The recommended initial regimen is 30–40 IU/kg twice weekly.
    - Based on the bleeding episodes:

- The regimen may be adjusted to 45–60 IU/kg every 5 days.
- A regimen may be further individually adjusted to less or more frequent dosing.

- **Koate (antihemophilic factor [human])**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous use after reconstitution only.
  - Each vial of KOĀTE contains the labeled amount of Factor VIII in international units (IU).
  - Required Dose (IU) = Body Weight (kg) x Desired Factor VIII Rise (IU/dL or % of normal) x 0.5
  - Frequency of KOĀTE administration is determined by the type of bleeding episode and the recommendation of the treating physician.

- **Kogenate FS (antihemophilic factor [recombinant], formulated with sucrose)**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous use only.
  - Each vial of Kogenate FS contains the labeled amount of recombinant factor VIII in international units (IU, unit)
  - Control and prevention of bleeding episodes and peri-operative management:
    - Dose (units) = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).
    - Titrate doses to patient's clinical response.
    - Determine treatment frequency based on type of bleeding episode.
  - For routine prophylaxis in adults:
    - 25 units per kg three times a week.
  - For routine prophylaxis in children:
    - 25 units per kg every other day.

- **Kovaltry (antihemophilic factor [recombinant])**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous use after reconstitution only.
  - Control of bleeding episodes and peri-operative management
    - Required dose (IU) = body weight (kg) x desired Factor VIII rise (% of normal or IU/dL) x reciprocal of expected/observed recovery (e.g., 0.5 for a recovery of 2 IU/dL per IU/kg).
    - Estimated Increment of Factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg).
  - Routine prophylaxis
    - Adults and adolescents: 20-40 IU/kg 2 or 3 times per week.
    - Children ≤12 years old: 25-50 IU/kg 2 times per week, 3 times per week or every other day.

- **Mononine (coagulation factor IX [human])**
  Mononine is intended for intravenous administration only.
  As a general rule, 1 IU of Factor IX activity per kg can be expected to increase the circulating level of Factor IX by 1% [IU/dL] of normal. The following formula provides a guide to dosage calculations:
  Number of Factor IX IU required (IU) = Body Weight (in kg) x desired Factor IX increase (% or IU/dL normal) x 1.0 U/kg [per IU/dL]

  The amount of Mononine to be infused, as well as the frequency of infusions, will vary with each patient and with the clinical situation.

  As a general rule, the level of Factor IX required for treatment of different conditions is as follows:

	Minor Spontaneous Hemorrhage, Prophylaxis	Major Trauma or Surgery
Desired levels of Factor IX for Hemostasis	15-25% [or IU/dL]	25-50% [or IU/dL]
Initial loading dose to achieve desired level	up to 20-30 IU/kg	up to 75 IU/kg
Frequency of dosing	once; repeated in 24 hours if necessary	every 18-30 hours, depending on $T_{1/2}$ and measured Factor IX levels
Duration of treatment	once; repeated if necessary	up to ten days, depending on nature of insult

Recovery of the loading dose varies from patient to patient. Doses administered should be titrated to the patient's response. Mononine administered in doses of ≥75 IU/kg were well tolerated.

In the presence of an inhibitor to Factor IX, higher doses of Mononine might be necessary to overcome the inhibitor (see PRECAUTIONS *[section of Prescribing Information]*). No data on the treatment of patients with inhibitors to Factor IX with Mononine are available.

- **Novoeight (antihemophilic factor [recombinant])**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous injection after reconstitution only.
  - Each vial of Novoeight contains the labeled amount of recombinant Factor VIII in international units (IU).
  - The required dosage is determined using the following formula:
    Dosage Required (IU) = Body Weight (kg) × Desired Factor VIII Increase (IU/dL or % normal) × 0.5 (IU/kg per IU/dL)
  - Frequency of Novoeight administration is determined by the type of bleeding episode and the recommendation of the treating physician.

- **NovoSeven RT (recombinant coagulation factor VIIa)**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous bolus injection only.

Bleeding Episodes:

Indication	Dosing Recommendation
Congenital Hemophilia A or B with Inhibitors	• 90 mcg/kg every 2 hours, adjustable based on severity of bleeding until hemostasis is achieved • 90 mcg/kg every 3-6 hours after hemostasis is achieved for severe bleeds
Acquired Hemophilia	• 70-90 mcg/kg every 2-3 hours until hemostasis is achieved
Congenital Factor VII Deficiency	• 15-30 mcg/kg every 4-6 hours until hemostasis is achieved
Glanzmann's Thrombasthenia	• 90 mcg/kg every 2-6 hours until hemostasis is achieved

Peri-operative Management:

Indication	Dosing Recommendation
Congenital Hemophilia A or B with Inhibitors	**Minor**: • 90 mcg/kg immediately before surgery, repeat every 2 hours during surgery • 90 mcg/kg every 2 hours after surgery for 48 hours, then every 2-6 hours until healing has occurred **Major**:

Indication	Dosing Recommendation
	• 90 mcg/kg immediately before surgery, repeat every 2 hours during surgery • 90 mcg/kg every 2 hours after surgery for 5 days, then every 4 hours until healing has occurred
Acquired Hemophilia	• 70-90 mcg/kg immediately before surgery and every 2-3 hours for the duration of surgery and until hemostasis is achieved
Congenital Factor VII Deficiency	• 15-30 mcg/kg immediately before surgery and every 4-6 hours for the duration of surgery and until hemostasis is achieved
Glanzmann's Thrombasthenia	• 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the procedure • 90 mcg/kg every 2-6 hours to prevent post-operative bleeding

- **Nuwiq (antihemophilic factor [recombinant])**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous use after reconstitution.
  - Each vial of NUWIQ is labeled with the actual amount of Factor VIII potency in international units (IU).
  - Determine dose using the following formula for adolescents and adults:
    Required IU = body weight (kg) x desired Factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL) (2)
  - Dosing for routine prophylaxis:

Subjects	Dose (IU/kg)	Frequency of infusions
Adolescents [12 - 17 yrs] and adults	30 - 40	Every other day.
Children [2 - 11 yrs]	30 - 50	Every other day or three times per week.

  - Frequency and duration of therapy depends on severity of the FVIII deficiency, location and extent of bleeding and patient's clinical condition.

- **Obizur (antihemophilic factor [recombinant], porcine sequence)**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous use after reconstitution only.
  - Initial dose of Obizur is 200 units per kg.
  - Titrate dose and frequency of administration based on factor VIII recovery levels and individual clinical response.

- **Profilnine (factor IX complex)**
  Each vial of Profilnine is labeled with total units expressed as International Units (IU). According to the WHO International Standard, one unit approximates the activity in one mL of normal plasma.

  A 1% increase in factor IX (0.01 units) per unit administered per kg body weight can be expected. The amount of Profilnine required to establish hemostasis will vary with each patient and circumstance. Use the following formula and example as guides in determining the number of units to be administered:

  Body Weight (in kg) x Desired increase in Plasma Factor IX (Percent) x 1 Units/kg = Number of Factor IX Units Required

  Example: 50 kg x 25 (% increase) x 1 Units/kg = 1,250 Units of Factor IX

Due to variability among patients and their clinical condition, monitor the factor IX level of each patient frequently during replacement therapy.

Table 2 below provides treatment guidelines for hemorrhagic events and surgery in patients with factor IX deficiency.

Table 2: Treatment Guidelines

Type of Bleeding or Surgical Procedure	Factor IX Level Required, % of Normal (Dose)	Frequency of Doses	Duration of Therapy (Days)
Minor to Moderate Hemorrhages	20-30% (20-30 IU FIX/kg) until hemorrhage stops and healing has been achieved.	Every 16-24 hrs	Minor: 1-2 days Moderate: 2-7 days
Major Hemorrhages	30-50% (30-50 IU FIX/kg). Following this treatment period, maintain FIX levels at 20% (20 IU FIX/kg) until healing has been achieved.	Every 16-24 hrs	3-10 days
Surgery	Prior to surgery, 30-50% (30-50 IU FIX/kg). For dental extractions, bring FIX levels to 50% immediately prior to the procedure. Maintain FIX levels at 30-50% (30-50 IU FIX/kg) until healing has been achieved.	Every 16-24 hrs	7-10 days

Dosing requirements and frequency of dosing are calculated on the basis of an initial response of 1% FIX increase achieved per IU of FIX infused per kg body weight and an average half-life for FIX of 24 hours. If dosing studies reveal that a particular patient exhibits a lower response, monitor blood levels and adjust the dose accordingly.

- **Rebinyn (factor IX, recombinant, glycoPEGylated)**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous infusion after reconstitution only.
  - Each carton and vial label for Rebinyn states the actual Factor IX potency in international units (IU).
  - Recommended dose for on-demand treatment and control of bleeding episodes: 40 IU/kg body weight for minor and moderate bleeds, and 80 IU/kg body weight for major bleeds. Additional doses of 40 IU/kg can be given.
  - Recommended dose for peri-operative management: Pre-operative dose of 40 IU/kg body weight for minor surgery, and 80 IU/kg body weight for major surgery. As clinically needed for the peri-operative management of bleeding, repeated doses of 40 IU/kg (in 1-3 day intervals) within the first week after major surgery may be administered. Frequency may be extended to once weekly after the first week until bleeding stops and healing is achieved.

- **Recombinate (antihemophilic factor [recombinant])**
  Each vial of Recombinate is labeled with the Factor VIII activity expressed in IU per vial. This potency assignment is referenced to the World Health Organization International Standard for Factor VIII:C Concentrate and is evaluated by appropriate methodology to ensure accuracy of the results.

  The expected *in vivo* peak increase in Factor VIII level expressed as IU/dL of plasma or % (percent) of normal can be estimated by multiplying the dose administered per kg body weight (IU/kg) by two. This calculation is based on the clinical findings of Abildgaard et al (N Eng J Med 1966; 275: 471-475) and is supported by the data generated by 419 clinical pharmacokinetic studies with Recombinate in 67 patients over time. This pharmacokinetic data demonstrated a peak recovery point above the pre-infusion baseline of approximately 2.0 IU/dL per IU/kg body weight.

Examples (Assuming patient's baseline Factor VIII level is at <1%):

1) A dose of 1750 IU Recombinate administered to a 70 kg patient, i.e. 25 IU/kg (1750 IU/70 kg), should be expected to cause a peak post-infusion Factor VIII increase of 25 IU/kg x 2 (IU/dL)/(IU/kg) = 50 IU/dL (50% of normal).
2) A peak level of 70% is required in a 40 kg child. In this situation, the dose would be 70 IU/dL/[2(IU/dL)/(IU/kg)] x 40 kg = 1400 IU.

Recommended Dosage Schedule
Physician supervision of the dosage is required. The following dosage schedule may be used as a guide.

Hemorrhage		
Degree of hemorrhage	**Required peak post infusion Factor VIII activity in the blood (as % of normal or IU/dL plasma)**	**Frequency of Infusion**
Early hemarthrosis or muscle bleed or oral bleed	20-40	Begin infusion every 12 to 24 hours for one-three days until the bleeding episode is resolved (as indicated by pain), or healing is achieved.
More extensive hemarthrosis, muscle bleed, or hematoma	30-60	Repeat infusion every 12 to 24 hours for (usually) three days or more until pain and disability are resolved.
Life threatening bleeds such as head injury, throat bleed, severe abdominal pain	60-100	Repeat infusion every 8 to 24 hours until threat is resolved
Surgery		
Type of Operation		
Minor surgery, including tooth extraction	60-80	A single infusion plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases.
Major surgery	80-100 (pre- and post-operative)	Repeat infusion every 8 to 24 hours depending on state of healing.

If bleeding is not controlled with the recommended dose, the plasma level of Factor VIII should be determined and a sufficient dose of Recombinate should be administered to achieve a satisfactory clinical response.

The careful control of the substitution therapy is especially important in cases of major surgery or life threatening hemorrhages. In presence of a low titer inhibitor, doses larger than those recommended may be necessary as per standard care.

Although dosage can be estimated by the calculations above, it is strongly recommended that whenever possible, appropriate laboratory tests including serial Factor VIII assays be performed on the patient's plasma at suitable intervals to assure that adequate Factor VIII levels have been reached and are maintained.

Patients should be evaluated for the development of Factor VIII inhibitors, if the expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose.

- **RiaSTAP (fibrinogen concentrate [human])**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For intravenous use only.
- Dose (mg/kg body weight) =

  $$\frac{\text{[Target level (mg/dL) - measured level (mg/dL)]}}{\text{1.7 (mg/dL per mg/kg body weight)}}$$
- Dose when fibrinogen level is unknown: 70 mg/kg body weight.
- Monitoring of patient's fibrinogen level is recommended during treatment. A target fibrinogen level of 100 mg/dL should be maintained until hemostasis is obtained.
- The injection rate should not exceed 5 mL per minute.

➢ **Rixubis (coagulation factor IX [recombinant])**

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For intravenous use after reconstitution only.
  On-demand treatment and control of bleeding episodes and peri-operative management of bleeding:
  - One international unit of RIXUBIS per kg of body weight increases the circulating activity of factor IX by 0.7 international units/dL for patients <12 years of age and 0.9 international units/dL for patients ≥12 years of age.
- *Initial Dose:*
  - Required international units = body weight (kg) × desired factor IX increase (% of normal or IU/dL) × reciprocal of observed recovery (IU/kg per IU/dL).
  - The maintenance dose depends on the type of bleed or surgery, the intensity of the hemostatic challenge, and number of days until adequate wound healing is achieved.

- *Routine prophylaxis:*
  - Patients <12 years of age: 60 to 80 international units per kg twice weekly
  - Patients ≥ 12 years of age: 40 to 60 international units per kg twice weekly.

➢ **Thrombate III (human antithrombin III)**

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For intravenous use after reconstitution only.
- Individualize dose to achieve AT level of 80 % to 120 % of normal human plasma.

Dose	Target AT Level	Dose (Units)	Monitor AT Level
Loading	120% of normal	120% - baseline % x body weight (kg) divided by 1.4%	• baseline • 20 minutes (peak) post-injection • 12 hours post-injection • pre-injection (trough)
Adjustment (as needed)	80% to 120% of normal	Target % - trough % x body weight (kg) divided by 1.4%	• 20 minutes (peak) post-injection • at least every 12 hours post-injection • pre-injection (trough)
Maintenance (every 24 hours as needed)	80% to 120% of normal	Loading Dose x 0.6	• approximately every 24 hours, as needed

➢ **Tretten (coagulation factor XIII A-subunit [recombinant])**

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For intravenous use only.
- Dose:
  - 35 international units per kilogram body weight once monthly to achieve a target trough level of FXIII activity at or above 10% using a validated assay.
  - Consider dose adjustment if adequate coverage is not achieved with a 35 IU/kg dose.
  - Once reconstituted, Tretten may be diluted with 0.9% sodium chloride to facilitate measurement of small volumes.

Rate: Do not exceed 1-2 mL per minute.

- **Vonvendi (von Willebrand factor, recombinant)**

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For intravenous use after reconstitution only
- On-demand Treatment and Control of Bleeding Episodes:
  - For each bleeding episode, administer the first dose of Vonvendi with an approved recombinant (non-von Willebrand factor containing) factor VIII if factor VIII baseline levels are below 40% or are unknown.
  - Initial dose is 40 to 80 international units (IU) per kg body weight. Adjust the dosage based on the extent and location of bleeding.

Hemorrhage	Initial Dose	Subsequent Dose
Minor	40 to 50 IU/kg	40 to 50 IU/kg every 8 to 24 hours (as clinically required)
Major	50 to 80 IU/kg	40 to 60 IU/kg every 8 to 24 hours for approximately 2 to 3 days (as clinically required)

- Peri-operative Management of Bleeding:

For elective surgical procedure:
  - A dose of Vonvendi may be given 12 to 24 hours prior to surgery to allow the endogenous factor VIII levels to increase to at least 30 IU/dL (minor surgery) or 60 IU/dL (major surgery).
  - Assess FVIII:C levels within 3 hours prior to surgery; If the FVIII:C levels are at or above the recommended minimum target levels, administer a dose of Vonvendi alone within 1 hour prior to the procedure. If the FVIII:C levels are below the recommended minimum target levels, administer recombinant factor VIII in addition to Vonvendi to raise VWF:RCo and FVIII:C.

For emergency surgery:
  - Assess baseline VWF:RCo and FVIII:C levels within 3 hours prior to surgery. If not available, use weight based dosing calculation.
  - Administer Vonvendi one hour before surgery with or without recombinant factor VIII and adjust the dose to raise VWF:RCo and FVIII:C to adequate level.

Type of Surgery	Target Peak Plasma Level		Calculation of rVWF Dose (IU VWF:RCo required)
	VWF:RCo	FVIII:C	
Minor	50 to 60 IU/dL	40 to 50 IU/dL	△ VWF:RCo × BW (kg) /IR
Major	100 IU/dL	80 to100 IU/dL	

- Continue to monitor the VWF:RCo and FVIII:C plasma levels after surgical procedure.

- **Wilate (human von Willebrand factor/coagulation factor VIII complex)**

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For Intravenous Use Only.

- Use the following formula to determine required dosage: Required IU = body weight (BW) in kg x desired VWF:RCo rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL)
- Adjust dosage and duration of the substitution therapy depending on the severity of the VWD, on the location and extent of the bleeding, and on the patient's clinical condition
- Dosing recommendations:

Type of Hemorrhages	Loading Dosage (IU VWF:RCo /kg BW)	Maintenance Dosage (IU VWF:RCo /kg BW)	Therapeutic Goal
Minor Hemorrhages	20-40 IU/kg	20-30 IU/kg every 12-24 hours	VWF:RCo and FVIII activity through levels of >30%
Major Hemorrhages	40-60 IU/kg	20-40 IU/kg every 12-24 hours	VWF:RCo and FVIII activity through levels of >50%
Minor Surgeries (including tooth extractions)	30-60 IU/kg	15-30 IU/kg or half the loading dose every 12-24 hours for up to 3 days	VWF:RCo peak level of 50% after loading dose and trough levels of > 30% during maintenance doses
Major Surgeries	40-60 IU/kg	20-40 IU/kg or half the loading dose every 12-24 hours for up to 6 days or more	VWF:RCo peak level of 100% after loading dose and trough levels of > 50% during maintenance doses

- In order to decrease the risk of peri-operative thrombosis, FVIII activity levels should not exceed 250%.

➢ **Xyntha (antihemophilic factor [recombinant])**

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For intravenous use after reconstitution only.
- The required dosage is determined using the following formula:
  Required units = body weight (kg) × desired factor VIII rise (IU/dL or % of normal) × 0.5 (IU/kg per IU/dL) where IU = International Unit
- Frequency of XYNTHA administration is determined by the type of bleeding episode and the recommendation of the treating physician.

Drug Availability

Product	Availability
Advate	Supplied in single-use vials containing nominally: 250, 500, 1000, 1500, 2000, 3000 or 4000 IU.
Adynovate	Supplied in single-use vials containing nominally (approximately) 250, 500, 750, 1000, 1500, 2000 or 3000 IU.
Afstyla	Supplied in single-use vials containing nominally 250, 500, 1000, 1500, 2000, 2500, or 3000 IU.
Alphanate	Supplied in single-dose vials containing 250, 500, 1000, 1500 IU or 2000 IU FVIII.
AlphaNine SD	Supplied in single-dose vials of 500 IU FIX/10 mL, 1000 IU FIX/10 mL, or 1500 IU FIX/10 mL.
Alprolix	Supplied in single-use vials containing nominally 250, 500, 1000, 2000, 3000, or 4000 IU.
ATryn	Supplied in a sterile lyophilized powder for reconstitution containing approximately 525 IU/vial.
BeneFIX	Supplied in single-use vials as 250, 500, 1000, 2000, or 3000 IU.
Coagadex	Supplied in single-use vials containing a nominal (approximately) 250 IU or 500 IU of Factor X activity.

Product	Availability
Corifact	Supplied in a vial containing 1000-1600 units lyophilized powder for reconstitution.
Eloctate	Supplied in single-use vials containing nominally: 250, 500, 750, 1000, 1500, 2000, 3000 4000, 5000 or 6000 IU.
Esperoct	Supplied in single-dose vials of dosage strengths at 500, 1000, 1500, 2000 and 3000 IU per vial.
FEIBA	Supplied in single-dose vials containing nominally 500, 1000, or 2500 units per vial.
Fibryga	Supplied in single-use bottles containing approximately 1 g fibrinogen concentrate per bottle.
Hemlibra	Supplied as a solution in single-dose vials in 30 mg/mL, 60 mg/0.4 mL, 105 mg/0.7 mL, or 150 mg/mL.
Hemofil M	Supplied as single-dose bottles that contain the following nominal potencies: 250 IU, 500 IU, 1000 IU, or 1700 IU.
Humate-P	Supplied in single-use vials that contain the labeled amount f VWF:RCo and FVIII activity expressed in IU. Refer to the product label for additional details.
Idelvion	Supplied in single-use vials containing nominally 250, 500, 1000, or 2000 IU.
Ixinity	Supplied in single-use vials containing nominally 250, 500, 1000, 1500, 2000, or 3000 IU per vial.
Jivi	Supplied in single-use vials containing nominally 500, 1000, 2000, or 3000 IU.
Koate	Supplied in single-use vials of 250, 500 or 1,000 international units of Factor VIII activity.
Kogenate FS	Supplied in single-use vials containing nominally: 250, 500, 1000, 2000, or 3000 IU.
Kovaltry	Supplied in single-use vials containing nominally: 250, 500, 1000, 2000, or 3000 IU.
Mononine	Supplied in a single-dose vial. Refer to the product label for additional details.
Novoeight	Supplied in single-use vials of 250, 500, 1000, 1500, 2000 or 3000 IU.
NovoSeven RT	Supplied in single-use vials of 1, 2, 5, or 8 mg recombinant coagulation factor VIIa.
Nuwiq	Supplied in single-use vials containing nominally: 250, 500, 1000 2000, 2500, 3000 or 4000 IU of Factor VIII potency.
Obizur	Supplied in single-use vials containing nominally 500 units per vial.
Profilnine	Supplied in single-dose vials available in the following potencies: 500 units FIX/5 mL; 1000 units FIX/10 mL; 1500 units FIX/10 mL.
Rebinyn	Supplied in single-use vials of 500, 1000, and 2000 IU.
Recombinate	Recombinate is supplied in single-dose vials in five different strengths. Refer to the product label for additional details.
RiaSTAP	Supplied as a single-use vial containing 900 mg to 1300 mg lyophilized fibrinogen concentrate powder for reconstitution.
Rixubis	Supplied in single-use vials containing nominally 250, 500, 1000, 2000, or 3000 IU.
Thrombate III	Supplied in a kit containing one single-use vial of Thrombate III lyophilized powder containing approximately 500 units, one vial of Sterile Water for Injection, USP, one sterile double-ended transfer needle, and one sterile filter needle.
Tretten	Supplied in single-use vial containing 2000-3125 IU of recombinant coagulation factor XIII A-subunit.
Vonvendi	Supplied in single-use vials containing nominally 650 or 1300 international units VWF:RCo.
Wilate	Supplied in vials for intravenous injection in the following strengths per vial: 500 IU VWF:RCo and 500 IU FVIII activities in 5 mL, 1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL.
Xyntha	Xyntha is supplied in single-use vials containing nominally: 250, 500, 1000, or 2000 IU.

Experimental, Investigational, or Unproven Uses

- **NovoSeven RT (recombinant coagulation factor VIIa)**

NovoSeven RT has being studied for use in hemorrhage in non-hemophilic individuals. At this time, however, there is insufficient published data in terms of safety and efficacy to support the use of NovoSeven RT for this indication.

A Cochrane systematic review evaluated the effectiveness of factor VII when used therapeutically to control active bleeding or as prophylaxis to prevent excessive bleeding in patients without hemophilia. Randomized controlled trials (RCTs) comparing factor VII with placebo or one dose of factor VII with another, in any non-hemophilia patients were included. Primary outcome was mortality. Secondary outcomes included blood loss or control of bleeding, red cell transfusion requirements, number of patients transfused and thromboembolic adverse events. A total of 29 (n = 4,290) RCTs were included – 16 trials (n = 1,361) examined prophylactic use of factor VII to prevent bleeding and 13 trials (n = 2,929) examined the therapeutic role of factor VII for the treatment of bleeding. The studies included trauma, cardio-pulmonary bypass, liver biopsy, partial hepatectomy, liver transplantation, pediatric craniofacial reconstruction, retropubic prostatectomy, burn patients requiring excision and grafting, pelvic fracture, and spinal fusion surgery. There was no effect on mortality in the prophylactic group as well as the therapeutic group. In both groups, modest benefits were found in the outcomes of blood loss and red cell transfusion requirements; however, these favorable findings were likely overestimated because data were not available from larger negative studies for inclusion in the meta-analysis. A statistically non-significant trend towards an increased risk of thromboembolic events with factor VII was observed. Results of this meta-analysis determined the effectiveness of factor VII, when used either prophylactically or therapeutically, in non-hemophilia patients remains unproven and the use of factor VII outside of its current licensed indications should be restricted to clinical trials. (Simpson, 2012)

An Agency for Healthcare Research and Quality comparative effectiveness review was conducted to examine patterns of off-label use of recombinant factor VIIa in the hospital setting and to evaluate evidence for 5 selected off-label indications (patients with/undergoing intracranial hemorrhage, massive bleeding from trauma, liver transplantation, cardiac surgery, and prostatectomy). The authors concluded that there is limited evidence and that the data available for recombinant factor VIIa does not demonstrate a reduction in mortality or improvement in other direct outcomes for the indications evaluated. Using recombinant factor VIIa in intracranial hemorrhage and adult cardiac surgery was associated with an increase in thromboembolic events. (Yank, 2010)

Coding/Billing Information

Note: Emicizumab-kxwh is typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes are generally not required for claims submitted under the pharmacy benefit plan. All other products in this policy are considered to fall under the medical benefit plan. They require medical drug coding and are listed as follows:

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Covered when medically necessary:

HCPCS Codes	Description
J7170	Injection, emicizumab-kxwh, 0.5 mg
J7175	Injection, factor X, (human), 1 IU
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 IU VWF:RCo
J7180	Injection, factor XIII (antihemophilic factor, human), 1 IU
J7181	Injection, factor XIII a-subunit, (recombinant), per IU
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), (Obizur), per IU

J7189	Factor VIIa (antihemophilic factor, recombinant), per 1 microgram
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
J7196	Injection, antithrombin recombinant, 50 IU
J7197	Antithrombin III (human), per IU
J7198	Anti-inhibitor, per IU
J7199	Hemophilia clotting factor, not otherwise specified
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 IU
J7203	Injection Factor IX, (antihemophilic factor, recombinant), glycoPEGylated, (Rebinyn), 1 IU
J7205	Injection, factor VIII Fc fusion, (recombinant), per IU
J7207	Injection, factor VIII, (antihemophilic factor, recombinant), pegylated, 1 IU
J7209	Injection, factor VIII, (antihemophilic factor, recombinant), (Nuwiq), 1 IU
J7210	Injection, factor VIII, (antihemophilic factor, recombinant), (Afstyla), 1 IU
J7211	Injection, factor VIII, (antihemophilic factor, recombinant), (Kovaltry), 1 IU

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