Drug and Biologic Coverage Policy

Effective Date 6/15/2024
Coverage Policy Number 8007

Clotting Factors and Antithrombin

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Related Coverage Resources

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®
- **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®
- **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) if BOTH of the following: o For use in surgical and/or invasive procedures o When there is a failure/inadequate response, contraindication, intolerance, not a candidate for, or inability to obtain BOTH of the following: ▪ Concentrated intranasal desmopressin (Stimate) ▪ Parenteral desmopressin (DDAVP injection) Alphanate is NOT indicated for severe VWD (type 3) undergoing major surgery.
ATryn [antithrombin III (recombinant)]	Prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient individuals
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
Hemofil M (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
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 • Treatment of spontaneous and/or trauma-induced bleeding episodes, or Prevention of excessive bleeding during and/or following surgery in EITHER of the following: o Mild to moderate VWD when there is failure/inadequate response, contraindication, intolerance, not a candidate for, or inability to obtain **BOTH** of the following: ▪ Concentrated intranasal desmopressin (Stimate) ▪ Parenteral desmopressin (DDAVP injection) o Severe VWD
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

Product	Criteria for Use
	• 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
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 • 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
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
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
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, intolerance, not a candidate for, or inability to obtain BOTH of the following: • Concentrated intranasal desmopressin (Stimate) Parenteral desmopressin (DDAVP injection)
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.

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.
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

Brand Name	Approved Indication(s)
	• 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.
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 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: • Treatment of spontaneous and trauma-induced bleeding episodes, and

Brand Name	Approved Indication(s)
	• 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.
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.

Brand Name	Approved Indication(s)
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.

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)

Professional Societies/Organizations for Management of Hemophilia A and B with Inhibitors
World Federation of Hemophilia (WFH) guidelines (2020) support recombinant Factor VIIa for patients with high-titer inhibitors who require acute treatment or around surgery/invasive procedures. (Srivastava, 2020) For low-titer inhibitors, Factor VIII or IX replacement may be used. These products may also be used for patients with a history of a high-titer inhibitor whose titer has fallen to low or undetectable levels. However, once an anamnestic response occurs, further treatment with Factor replacement is typically no longer effective, and bypass agent therapy (e.g., recombinant Factor VIIa) is needed. National Hemophilia Foundation MASAC guidelines (updated February 2020) have similar recommendations: treatment for patients with inhibitors depends on multiple factors, including type of inhibitor (high- or low-responding), current titer, location of bleed, and previous response. (MASAC, 2020)

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)**

Brand Name	Approved Indication(s)
	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.
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)

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.

➢ **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.

➢ **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).

➢ **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	$\frac{\Delta^* \text{ VWF:RCo} \times \text{BW (kg)}}{\text{IVR}^{\varepsilon}}$ = IU VWF:RCo required
Minor/Oral Surgery±	$\frac{\Delta^* \text{ VWF:RCo} \times \text{BW (kg)}}{\text{IVR}}$ = 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.

➢ **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.

- **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.

➢ **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.

➢ **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.

- **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

- **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.

Product	Availability
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.
ATryn	Supplied in a sterile lyophilized powder for reconstitution containing approximately 525 IU/vial.
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.
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.
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.
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.
Recombinate	Recombinate is supplied in single-dose vials in five different strengths. Refer to the product label for additional details.
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.
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.

Coding/Billing Information

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.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J7178	Injection, human fibrinogen concentrate, not otherwise specified, 1 mg
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
J7196	Injection, antithrombin recombinant, 50 IU
J7197	Antithrombin III (human), per IU
J7198	Anti-inhibitor, per IU
J7199	Hemophilia clotting factor, not otherwise specified
J7204	Injection, factor VIII, antihemophilic factor (recombinant), (esperoct), glycopegylated-exei, per iu
J7205	Injection, factor VIII Fc fusion, (recombinant), per IU
J7207	Injection, factor VIII, (antihemophilic factor, recombinant), pegylated, 1 IU
J7208	Injection, Factor VIII, (antihemophilic factor, recombinant), PEGylated-aucl, (Jivi), 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

References

1. Advate (antihemophilic factor [recombinant]) [product information]. Westlake Village, CA: Baxalta US Inc. December 2018.
2. Adynovate (antihemophilic factor (recombinant), pegylated [product information]. Lexington, MA: Baxalta US Inc. May 2018.
3. Afstyla (antihemophilic factor [recombinant], single chain) [product information]. Kankakee, IL: CSL Behring LLC. December 2019.
4. Alphanate (antihemophilic factor/von Willebrand factor complex [human]) [product information]. Los Angeles, CA: Grifols Biologicals Inc. March 2017.
5. AlphaNine SD (coagulation factor IX [human]) [product information]. Los Angeles, CA: Grifols Biologicals Inc. March 2017.
6. Alprolix (coagulation factor IX [recombinant], Fc fusion protein) [product information]. Cambridge, MA: Biogen Idec Inc. April 2017.
7. American Society of Hematology. 2012 Clinical Practice Guideline on the Evaluation and Management of von Willebrand Disease (VWD). Adapted from Nichols WL, Hultin MB, James AH et al. The Diagnosis, Evaluation, and Management of von Willebrand Disease. National Heart, Lung, and Blood Institute, NIH Pub. No. 08-5832. December 2007.
8. ATryn (antithrombin [recombinant]) [product information]. Framingham, MA: rEVO Biologics, Inc. December 2013.
9. BeneFIX (coagulation factor IX [recombinant]) [product information]. Philadelphia, PA: Wyeth Pharmaceuticals Inc. July 2019.
10. Centers for Disease Control and Prevention. Hemophilia: Inhibitors. http://www.cdc.gov/ncbddd/hemophilia/inhibitors.html. Updated February 9, 2016 Accessed February 19, 2016.
11. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Anti-Inhibitor Coagulant Complex (AICC) (110.3); version number 1. Available at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=150&ver=1. Accessed 2/4/2019.
12. Eloctate (antihemophilic factor [recombinant], Fc fusion protein) [product information]. Cambridge, MA: Biogen Iden Inc. January 2017.
13. Esperoct lyophilized powder for solution for intravenous use [product information]. Plainsboro, NJ: Novo Nordisk; February 2019.
14. Hemofil M (human plasma-derived) [product information]. Deerfield, IL: Baxter Healthcare Corporation. June 2018.
15. Holbrook A, Schulman S, Witt DM, et al, American College of Chest Physicians. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141 (2 Suppl): e152S-e184S.
16. Humate-P (antihemophilic factor/von Willebrand factor complex [human]) [product information]. Kankakee, IL: CSL Behring LLC. September 2017.
17. Idelvion (coagulation factor IX [recombinant], albumin fusion protein) [product information]. Kankakee, IL: CSL Behring LLC. October 2019.

18. Ixinity (coagulation factor IX [recombinant]) [product information]. Baltimore, MD: Cangene bioPharma, Inc. December 2018.
19. Jivi (antihemophilic factor (recombinant), PEGylated-aucl] lyophilized powder for solution, for intravenous use (package insert). Whippany, NJ: Bayer HealthCare LLC.; August 2018.
20. Koate (Antihemophilic Factor [Human]) [prescribing information]. Fort Lee, NJ: Kedrion Biopharma Inc; June 2018.
21. Kogenate FS (antihemophilic factor [recombinant], formulated with sucrose) [product information]. Tarrytown, NY: Bayer HealthCare LLC. May 2016.
22. Kovaltry (antihemophilic factor [recombinant]) [product information]. Tarrytown, NY: Bayer HealthCare LLC. March 2016.
23. McEvoy GK, ed. AHFS 2018 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc. 2018.
24. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised April 2018). MASAC Document #253. Adopted April 2018. Available at: https://www.hemophilia.org/sites/default/files/document/files/masac253.pdf. Accessed on February 13, 2020.
25. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised February 2020). MASAC Document #259. Available at: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/MASAC-Recommendations-Concerning-Products-Licensed-for-the-Treatment-of-Hemophilia-and-Other-Bleeding-Disorders. Accessed on August 21, 2020.
26. Mononine (coagulation factor IX [human]) [product information]. Kankakee, IL: CSL Behring LLC. December 2018.
27. National Hemophilia Foundation. Types of Bleeding Disorders. http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=179&contentid=45&rptname=bleeding. Accessed February 8, 2018
28. Novoeight (antihemophilic factor [recombinant]) [product information]. Plainsboro, NJ: Novo Nordisk Inc. November 2018.
29. Nuwiq (antihemophilic factor [recombinant]) [product information]. Hoboken, NJ: Octapharma USA, Inc. July 2017.
30. Obizur (antihemophilic factor [recombinant], porcine sequence) [product information]. Lexington, MA: Baxalta US Inc. January 2020.
31. Pal N, Kertai MD, Lakshminarasimhachar A, and Avidan MS. Pharmacology and clinical applications of human recombinant antithrombin. Expert Opin Biol Ther 2010; 10 (7): 1155-68.
32. Profilnine (factor IX complex) [product information]. Los Angeles, CA: Grifols Biologicals Inc. May 2017.
33. Rebinyn (factor IX, recombinant, glycoPEGylated) [product information]. Plainsboro, NJ: Novo Nordisk Inc. August 2022.
34. Recombinate (antihemophilic factor [recombinant]) [product information]. Lexington, MA: Baxalta. June 2018.
35. Rixubis (coagulation factor IX [recombinant]) [product information]. Westlake Village, CA: Baxter Healthcare Corporation. December 2019.
36. Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD005011. DOI: 10.1002/14651858.CD005011.pub4.
37. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition [published online ahead of print, 2020 Aug 3]. *Haemophilia*. 2020;10.1111/hae.14046.
38. Thrombate III (antithrombin III [human]) [product information]. Research Triangle Park, NC: Grifols Therapeutics Inc. January 2019.
39. Wilate (von Willebrand factor/coagulation factor VIII complex [human]) [product information]. Hoboken, NJ: Octapharma USA Inc. September 2016.
40. Xyntha (antihemophilic factor [recombinant]) [product information]. Philadelphia, PA: Wyeth Pharmaceuticals Inc. August 2019.
41. Yank V, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, Sundaram V, McMahon D, Stave CD, Zehnder JL, Olkin I, McDonald KM, Owens DK, Stafford RS. Comparative Effectiveness of Recombinant Factor VIIa for Off-Label Indications vs. Usual Care. Comparative Effectiveness Review No. 21. (Prepared by Stanford-UCSF Evidence-based Practice Center under Contract No. #290-02-0017) Rockville, MD:

Agency for Healthcare Research and Quality. May 2010. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.