# Hemophilia and Related Agents
# Therapeutic Class Review (TCR)

**September 1, 2020**



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# FDA-APPROVED INDICATIONS

## Factor VIII Products

| Drug | Manufacturer | Indications |
|---|---|---|
| antihemophilic factor VIII - recombinant (Advate®)[1] | Baxalta | • Control and prevention of bleeding episodes in adults and children with hemophilia A (classical hemophilia)<br>• Perioperative management in adults and children with hemophilia A<br>• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A<br>• Not indicated for von Willebrand disease (vWD) |
| antihemophilic factor VIII – recombinant, PEGylated (Adynovate®)[2] | Baxalta | • Control and prevention of bleeding episodes in adults and adolescents 12 years and older with hemophilia A<br>• Perioperative management in adults and children with hemophilia A<br>• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A<br>• Not indicated for vWD |
| antihemophilic factor VIII – recombinant, single chain (Afstyla®)[3] | CSL Behring | • Prevention and control of bleeding episodes in adults and children with hemophilia A<br>• Perioperative management in adults and children with hemophilia A<br>• Routine prophylaxis therapy to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A<br>• Not indicated for vWD |
| antihemophilic factor VIII – plasma derived (Alphanate®)[4] | Grifols | • Control and prevention of bleeding episodes in hemophilia A<br>• Surgical and/or invasive procedures in adult and pediatric patients with vWD in whom desmopressin is ineffective or contraindicated; it is not indicated for patients with severe vWD (type 3) undergoing major surgery |
| antihemophilic factor VIII – recombinant, FC fusion protein (Eloctate®)[5] | Bioverativ Therapeutics | • Prevention and control of bleeding episodes in adults and children with hemophilia A<br>• Perioperative management in adults and children with hemophilia A<br>• Routine prophylaxis therapy to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A<br>• Not indicated for vWD |
| antihemophilic factor – recombinant, glycopegylated-exei (coagulation factor VIII concentrate) (Esperoct®)[6] | Novo Nordisk | • On-demand treatment and control of bleeding episodes in adults and children with hemophilia A<br>• Perioperative management of bleeding in adults and children with hemophilia A<br>• Routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia A<br>• Not indicated for the treatment of vWD |
| antihemophilic factor VIII – plasma derived (Hemofil M®)[7] | Baxalta | • Control and prevention of hemorrhagic episodes in hemophilia A<br>• Not indicated for vWD |

### *Factor VIII Products (continued)*

| Drug | Manufacturer | Indications |
|---|---|---|
| antihemophilic factor VIII – plasma derived (Humate-P®)[8] | CSL Behring | • Treatment and prevention of bleeding in adults with hemophilia A<br>• Treatment of spontaneous and trauma-induced bleeding episodes, and prevention of excessive bleeding during and after surgery for adults and pediatric patients with vWD; this applies to patients with severe and mild to moderate vWD where the use of desmopressin is known or suspected to be inadequate<br>• Not indicated for the prophylaxis of spontaneous bleeding episodes in vWD |
| antihemophilic factor VIII – recombinant, PEGylated (Jivi®)[9] | Bayer Healthcare | • Control and prevention of bleeding episodes in adults and adolescents 12 years and older with hemophilia A<br>• Perioperative management in adults and adolescents 12 years and older with hemophilia A<br>• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and adolescents 12 years and older with hemophilia A<br>• Not indicated for use in previously untreated patients<br>• Not indicated for vWD |
| antihemophilic factor VIII – plasma derived (Koate DVI®)[10] | Grifols Therapeutics (distributed by Kedrion Biopharma) | • Treatment of hemophilia A in which there is a demonstrated deficiency of activity of the plasma clotting factor VIII to control or prevent bleeding episodes, or in order to perform emergency and elective surgery on individuals with hemophilia<br>• Not approved for use in vWD |
| antihemophilic factor VIII – recombinant (Kogenate FS®)[11,12] | Bayer Healthcare | • Control and prevention of bleeding episodes in adults and children with hemophilia A<br>• Perioperative management in adults and children with hemophilia A<br>• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in children with hemophilia A and reduce the risk of joint damage in children showing no preexisting joint damage<br>• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults with hemophilia A<br>• Not indicated for vWD |
| antihemophilic factor VIII – recombinant (Kovaltry®)[13,14] | Bayer Healthcare | • Control and prevention of bleeding episodes in adults and children with hemophilia A<br>• Perioperative management of bleeds in adults and children with hemophilia A<br>• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults with hemophilia A<br>• Not indicated for vWD |
| antihemophilic factor VIII – recombinant (Novoeight®)[15] | Novo Nordisk | • On-demand treatment and control of bleeding episodes in adults and children with hemophilia A<br>• Perioperative management in adults and children with hemophilia A<br>• Routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia A<br>• Not indicated for vWD |

### *Factor VIII Products (continued)*

| Drug | Manufacturer | Indications |
|---|---|---|
| antihemophilic factor VIII – recombinant (Nuwiq®)[16] | Octapharma | • Control and prevention of bleeding episodes in adults and children with hemophilia A<br>• Perioperative bleed management in adults and children with hemophilia A<br>• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A<br>• Not indicated for vWD |
| antihemophilic factor VIII – recombinant, porcine sequence (Obizur®)[17] | Baxalta | • For the on-demand treatment and control of bleeding episodes in adults with acquired hemophilia A<br>• Safety and efficacy have not been established in patients with a baseline anti-porcine factor VIII inhibitor titer of greater than 20 BU<br>• Not indicated for the treatment of congenital hemophilia A or vWD |
| antihemophilic factor VIII – recombinant (Recombinate®)[18] | Baxalta | • Control and prevention of hemorrhagic episodes in hemophilia A in adults and children<br>• Perioperative management in patients with hemophilia A<br>• Not indicated for vWD |
| antihemophilic factor VIII – recombinant (Xyntha®)[19,20] | Wyeth/Pfizer | • Control and prevention of bleeding episodes in adults and children with hemophilia A<br>• Perioperative management in adults and children with hemophilia A<br>• For routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia A<br>• Not indicated for vWD |

## Factor IX Products

| Drug | Manufacturer | Indications |
|---|---|---|
| coagulation factor IX – plasma derived (AlphaNine SD®)[21] | Grifols | • Prevention and control of bleeding in patients greater than 16 years of age with factor IX deficiency due to hemophilia B<br>• AlphaNine SD contains low, non-therapeutic levels of factors II, VII, and X, and is not indicated for the treatment of factor II, VII, or X deficiencies<br>• Not indicated for the treatment of hemophilia A patients with inhibitors to factor VIII |
| coagulation factor IX – recombinant, FC fusion protein (Alprolix®)[22] | Bioverativ | • Prevention and control of bleeding episodes in adults and children with factor IX deficiency, hemophilia B<br>• Perioperative management in adults and children with hemophilia B<br>• Routine prophylaxis therapy to prevent or reduce the frequency of bleeding episodes in adults and children with factor IX deficiency, hemophilia B<br>• Not indicated for induction of immune tolerance therapy in patients with hemophilia B |
| coagulation factor IX – recombinant (BeneFIX®)[23] | Wyeth/Pfizer | • On-demand treatment and control of bleeding episodes in adults and pediatric patients with hemophilia B<br>• Perioperative management of bleeding in adults and pediatric patients with hemophilia B<br>• Routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia B<br>• Not indicated for induction of immune tolerance in patients with hemophilia B or the treatment of hemophilia A |

***Factor IX Products (continued)***

| Drug | Manufacturer | Indications |
|---|---|---|
| coagulation factor IX – recombinant, albumin fusion protein (Idelvion®)[24] | CSL Behring | • Prevention and control of bleeding episodes in adults and children with hemophilia B<br>• Perioperative management in adults and children with hemophilia B<br>• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia B<br>• Not indicated for induction of immune tolerance therapy in patients with hemophilia B |
| coagulation factor IX – recombinant (Ixinity®)[25] | Aptevo BioTherapeutics | • Prevention and control of bleeding episodes in adults and pediatric patients 12 years of age or older with hemophilia B<br>• Perioperative management in adults and pediatric patients with hemophilia B<br>• Not indicated for the induction of immune tolerance therapy in patients with hemophilia B |
| coagulation factor IX – plasma derived (Mononine®)[26] | CSL Behring | • Prevention and control of bleeding in factor IX deficiency, also known as hemophilia B<br>• Not indicated in the treatment or prophylaxis of hemophilia A in patients with inhibitors to factor VIII<br>• Not indicated for treatment of or reversal of coumarin-induced anticoagulation<br>• Mononine contains non-detectable levels of factors II, VII, and X and is, therefore, not indicated for replacement therapy of these clotting factors |
| coagulation factor IX – plasma derived (Profilnine SD®)[27] | Grifols | • Prevention and control of bleeding in patients with factor IX deficiency due to hemophilia B<br>• Not indicated for use in the treatment of factor VII deficiency |
| coagulation factor IX – recombinant, PEGylated (Rebinyn®)[28] | Novo Nordisk | • Prevention and control of bleeding episodes in adults and children with factor IX deficiency, hemophilia B<br>• Perioperative management in adults and children with hemophilia B<br>• Not indicated for routine prophylaxis therapy in adults and children with factor IX deficiency, hemophilia B<br>• Not indicated for induction of immune tolerance therapy in patients with hemophilia B |
| coagulation factor IX – recombinant (Rixubis®)[29] | Baxalta | • Prevention and control of bleeding episodes in adults and children with factor IX deficiency, hemophilia B<br>• Perioperative management in adults and children with hemophilia B<br>• Routine prophylaxis therapy to prevent or reduce the frequency of bleeding episodes in adults and children with factor IX deficiency, hemophilia B<br>• Not indicated for induction of immune tolerance therapy in patients with hemophilia B |

Bebulin®, by Shire, has been discontinued due to reduced demand of the product. All product expired by November 2018.[30]

CSL Behring discontinued distribution of Monoclate P®; supply was estimated to be depleted by December 2018.[31]

CSL Behring discontinued Hexilate FS in 2018; supply was anticipated to be exhausted in early 2019.[32]

## Factor VIIa and Activated Prothrombin Complex Concentrate Products

| Drug | Manufacturer | Indications |
|---|---|---|
| activated prothrombin complex - plasma derived (Feiba®)[33] | Baxalta | • Control and prevention of bleeding episodes in hemophilia A and hemophilia B patients with inhibitors<br>• Perioperative management in hemophilia A and hemophilia B patients with inhibitors<br>• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia A and hemophilia B patients with inhibitors<br>• Not indicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to factor VIII or factor IX |
| coagulation factor VIIa - recombinant (NovoSeven RT®)[34] | Novo Nordisk | • Treatment of bleeding episodes in hemophilia A or B with inhibitors and in acquired hemophilia<br>• Prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B with inhibitors and in acquired hemophilia<br>• Treatment of bleeding episodes in congenital factor VII (FVII) deficiency<br>• Prevention of bleeding in surgical interventions or invasive procedures in congenital FVII deficiency<br>• Treatment of Glanzmann's Thrombasthenia with refractoriness to platelet transfusions with or without antibodies |

## Factor IXa and Factor X Directed Antibody Products

| Drug | Manufacturer | Indications |
|---|---|---|
| emicizumab-kxwh (Hemlibra®)[35] | Genentech | • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A with or without factor VIII inhibitors |

## Factor X and Factor XIII Products

| Drug | Manufacturer | Indications |
|---|---|---|
| coagulation factor X - plasma derived (Coagadex®)[36] | Bio Products Laboratory | • Routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with heredity factor X deficiency<br>• On-demand treatment and control of bleeding episodes in adults and children with heredity factor X deficiency<br>• Perioperative management of bleeding in patients with mild and moderate hereditary factor X deficiency in adults and children with heredity factor X deficiency<br>• Not studied in the perioperative management of bleeding in major surgery in patients with severe hereditary Factor X deficiency |
| coagulation factor XIII – plasma derived (Corifact®)[37] | CSL Behring | • Routine prophylactic treatment for adult and pediatric patients with congenital factor XIII deficiency<br>• Perioperative management of surgical bleeding in adult and pediatric patients with congenital XIII deficiency |
| coagulation factor XIII A-subunit– recombinant (Tretten®)[38] | Novo Nordisk | • Routine prophylaxis of bleeding in patients with congenital factor XIII A-subunit deficiency<br>• Not indicated for use in patients with congenital factor XIII B-subunit deficiency |

## Von Willebrand Products

| Drug | Manufacturer | Indications |
|---|---|---|
| von Willebrand factor - recombinant (Vonvendi®)[39] | Baxalta | • For on-demand treatment and control of bleeding episodes in adults (age 18 and older) with vWD<br>• Perioperative management of bleeding in adults (age 18 and older) with vWD |
| von Willebrand factor/coagulation factor VIII complex –plasma derived (Wilate®)[40] | Octapharma | • For on-demand treatment and control of bleeding episodes in children and adults with vWD<br>• Perioperative management of bleeding in children and adults with vWD<br>• Routine prophylaxis to reduce the frequency of bleeding episodes in adolescents and adults with hemophilia A<br>• For on-demand treatment and control of bleeding episodes in adolescents and adults with hemophilia A |

## OVERVIEW[41,42,43,44,45,46,47,48,49,50,51,52]

Hemophilia is a rare, inherited bleeding disorder where the blood does not clot properly due to an absence of 1 of the coagulation factors present in normal blood. Hemophilia is identified as an X-linked congenital bleeding disorder that has an estimated frequency of 1 in 5,000 to 10,000 births. The World Federation of Hemophilia estimates the global prevalence of hemophilia at around 400,000 persons. It is estimated there are approximately 20,000 persons in the United States are afflicted with hemophilia.

The term hemophilia is commonly believed to reference hemophilia type A or B which involve deficiencies in factor VIII (8) or IX (9); however, the term also encompasses a number of other rare factor deficiencies. These disorders include deficiencies involving the following factors: factor I (1) – fibrinogen deficiency; factor II (2) – prothrombin deficiency; factor V (5) – proconvertin deficiency; factor X (10) – Stuart-Prower deficiency; factor XI (11) – hemophilia C or plasma thromboplastin deficiency; factor XII (12) – Hageman factor deficiency; and factor XIII (13) fibrin stabilizing deficiency. These disorders are far less common than hemophilia A and B, exemplified by factor XIII deficiency which is estimated to occur in 1 in 2 to 5 million persons. Many of these diseases also have specialized treatments. The factor product Coagadex is only indicated for the treatment of congenital factor X deficiency, while Corifact and Tretten are only indicated for the treatment of congenital factor XIII deficiency. The focus of the remainder of this review will be on hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency).

Patients born with hemophilia may have varying degrees of coagulation or clotting factor deficiencies which serve to characterize the severity of their disease. There are 2 main types of hemophilia, type A and type B. Patients with type A hemophilia exhibit low or missing levels of clotting factor VIII (8), while those with type B have low or missing levels of clotting factor IX (9). Hemophilia A is also known as factor VIII deficiency, classical hemophilia, or standard hemophilia. Hemophilia B is also known as factor IX deficiency or Christmas disease. Hemophilia A is far more common than hemophilia B with hemophilia A presenting in 80% to 85% of all hemophilia patients. Hemophilia also typically affects males on the maternal side due to X-linked inheritance; however, females may also rarely be affected but are more commonly carriers of the disease. Up to 30% of newly diagnosed cases occur with no prior family history and are attributed to spontaneous mutations in either the F8 or F9 gene. While a diagnosis of hemophilia may be made from specific tests from an umbilical cord blood sample if there is a family history or suspicion of hemophilia, the disease is more commonly diagnosed when a

recurrence of excessive bleeding problems is noted. The extent of bleeding episodes depends on the severity of hemophilia and these may be instances of external or internal bleeding. Persons who have mild hemophilia may not normally exhibit problems with clotting until after occurrences such as dental procedures, surgery, or an accident. More commonly, signs of hemophilia leading to a positive diagnosis include external bleeds such as: mouth bleeds following a cut, losing a tooth or teething; heavy bleeding from minor cuts; bleeding from cuts that resume after short stoppages; and bleeding following circumcision. Internal signs of excessive bleeding that may indicate hemophilia include: easy and large areas of bruising, particularly in the large muscles of the body; spontaneous bleeding into joints (knees, elbows, and ankles), muscles, and soft tissues; joints that suddenly swell, are hot to the touch, and painful; blood in the stool or urine; long-lasting painful headaches; neck stiffness; double vision; repeated vomiting; and convulsions or seizures. Bleeding manifestations can lead to substantial morbidity, as well as mortality, if not properly treated.

Hemophilia, regardless of type (hemophilia A or B), is classified as mild, moderate, or severe depending on the intrinsic amount of clotting factor, either factor VIII or factor IX, in the patient's blood. The following table details the severity, general clotting factor level, and bleeding episode characteristics for hemophilia. Bleeding into joints or hemarthrosis is more common than bleeds into muscles, the central nervous system, or other major bleeds and comprise between 70% to 80% of bleeds. Bleeding is more common in hinged joints, such as ankles, elbows, and knees, and less frequent on multi-axial joints, such as hips, shoulders, and wrists. Frequent and prolonged bleeds in the hinged joints may cause these to become less functional over time.

| Severity | Level of Clotting Factor | Bleeding Characteristics |
|---|---|---|
| Mild hemophilia | 5% to < 40% of normal<br>(5 to 40 IU/dL) | Patient may never exhibit bleeds; spontaneous bleeds are rare; rarely has joint problems; may have severe bleeding with surgery, injections, or major trauma |
| Moderate hemophilia | 1% to 5% of normal<br>(1 to 5 IU/dL) | Patient may have rare or occasional spontaneous bleeds; may have prolonged bleeds with minor trauma or surgery; may experience joint problems |
| Severe hemophilia | < 1% of normal<br>(< 1 IU/dL) | Patient can experience spontaneous bleeds without injury; joint and muscle bleeds are common; may experience bleeds 1 to 2 times a week |

In August 2020, the World Federation of Hemophilia published its comprehensive treatment guidelines for the disease. The guidelines list the general principles of care for treatment of bleeding episodes. These include the prevention and treatment of bleeds with the specific factor concentrate for that patient's clotting deficiency; treatment of active bleeds as soon as possible; help in teaching patients to recognize a bleeding aura which is often experienced prior to outward evidence of a bleed; the use of adjunctive therapies to help control bleeds, including compression and cold therapy; ensuring that patients seek experienced medical care, including a pediatric or adult hematologist and continuing care through a recognized hemophilia treatment center; use of patient training and home therapy to treat non-life-threatening bleeding episodes; comprehensive care plans that encourage and promote regular exercise to improve overall fitness while avoiding activities likely to cause trauma; maintaining good oral health and regular appointments to monitor health status.

The recommended treatment of bleeding episodes is dependent on several factors, including the patient's severity level, the location, and type of the injury or trauma, as well as the patient's overall status. Providing immediate treatment reduces the risk of lasting damage, the need for additional

medication, and the reduction of pain, as well as additional treatments. It is important to note that a person with a bleeding disorder will not bleed faster than anyone else; however, the bleeding, if untreated, will last longer. The updated 2020 guidelines are more comprehensive than prior editions, and include new chapters on genetic assessment; prophylaxis with hemostatic agents for prevention of bleeding; management of patients with inhibitors; outcome assessment, as well as the principles of managing hemophilia to provide benchmarks for care.

The National Hemophilia Foundation Medical and Safety Advisory Committee (MASAC) published a revised document (#259) with recommendations regarding products used for the treatment of hemophilia and other bleeding disorders in March 2020. The recommendations maintain the position that the risk of human viral contamination associated with recombinant factor VIII products is very low. It is again acknowledged that there have been no reported instances of seroconversion of human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) with recombinant derived products. Recombinant factor VIII products are the recommended treatment of choice by MASAC for patients with hemophilia A. MASAC also recommended that manufacturers should work toward the removal of human albumin, as well as human and/or bovine proteins, from their manufacturing processes for the recombinant factor VIII products.

The MASAC recommendations address the use of plasma-derived factor VIII products. The MASAC recommendations stated improved purification and viral-depleting processes along with increased donor screening processes have greatly reduced the risk of transmission from plasma-derived factor products of HIV, HBV, and HCV. There have not been any reported instances of seroconversion of HIV, HBV, or HCV as a result of the use of any plasma-derived factor VIII products currently available in the United States. This includes products that undergo the following purification/viral inactivation measures: dry-heated; heating in aqueous solution (pasteurization); solvent-detergent treatment; and/or immunoaffinity chromatography purification. Each of these methods, whether employed alone or in conjunction with another process, appears to have greatly reduced the risk of viral transmission compared to older methods. Despite the improvements and lack of any documented transmission, MASAC maintains there remains a possibility of HIV, HBV, or HCV virus transmission with the use of currently marketed, viral-inactivated, plasma-derived products. The MASAC guidelines also caution that other non-lipid enveloped viruses may also be transmitted by plasma-derived factor VIII products; MASAC acknowledges that additional measures have been taken, such as viral filtration, to further reduce any potential transmission risks.

Similar to the recommendations for factor VIII products, MASAC stated that recombinant factor IX products should also be considered the treatment of choice for hemophilia B patients due to the greatly reduced pathogen transmission risk compared with the plasma-derived factor IX concentrates.

The factor product table located in the *Dosages* section of this review contains information about purification methods utilized by the various factor products, both recombinant and plasma-derived.

In May of 2016, the results of the SIPPET trial (Survey of Inhibitors in Plasma Products Exposed Toddlers) was published in the *New England Journal of Medicine*. The SIPPET trial was a prospective randomized study of previously-untreated patients occurring between January 2010 and December 2014 that collected data from a large multi-national group of patients with hemophilia A. In the study, one-half of the patients were randomized to receive either recombinant or plasma-derived factor VIII products containing von Willebrand factor (vWF). The authors' reported results indicated there was a significantly higher incidence of neutralizing antibodies (inhibitor development), 87%, from the use of

recombinant factor VIII products than occurred with plasma-derived products. Overall in the study, there was an inhibitor development rate of 26.8% among patients. In June of 2016, MASAC addressed the findings of the SIPPET trial. The MASAC response noted some differences in United States' treatment experiences than those found in other geographical areas involved in the study. The differences included, but were not limited to: greater use of third generation factor VIII products than available in SIPPET; higher incidence of prophylactic treatment in the United States than seen in the study; and potential increases in inhibitor detection because of the threshold level established in the study. MASAC also continued to stress that there was a theoretical increased risk of viral transmission with plasma-derived products versus possible increased risk of inhibitors with recombinant factor agents and patients/providers should weigh these risks. Based on the current data available, MASAC acknowledged that there is no blanket recommendation regarding product selection in any given patient and recommended that patients currently undergoing treatment continue with their factor selection, while those just beginning therapy consider all potential risks prior to selecting a recombinant or plasma-derived factor product.

In March 2020, MASAC published recommendations regarding the use and management of hemophilia A with emicizumab-kxwh (Hemlibra) in patients with and without inhibitors. Hemlibra is a recombinant, humanized, bispecific immunoglobulin G4 monoclonal antibody and is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children of all ages, newborn and older, with hemophilia A with and without factor VIII inhibitors. It is structurally and functionally different from factor VIII and has demonstrated a substantial decrease in annualized bleeding rates. Hemlibra is administered subcutaneously as a loading dose of 3 mg/kg for 4 doses weekly, followed by 1 of 3 maintenance dosing schedules (weekly, every 2 weeks, or every 4 weeks). The MASAC recommendations state that patients with an inhibitor who are experiencing frequent bleeding episodes and are receiving either episodic therapy or bypassing agent (BPA) prophylaxis are expected to receive substantial benefit; in these patients, it should be considered first-line therapy. A switch to Hemlibra may also be considered for patients currently on BPA prophylaxis with few bleeding episodes, depending on a comparison with current BPA prophylaxis therapy (cost, administration factors). Infants should be considered for using Hemlibra for prophylaxis beginning after birth due to the potential for intracranial hemorrhage before factor VIII prophylaxis is started; however, limited data are available regarding use in patients younger than 6 months and drug levels are anticipated to be decreased, compared to older patients. In general, patients of any age or severity of hemophilia A with or without inhibitors may be appropriate candidates for Hemlibra taking into consideration the benefits and risks of this novel agent compared to their current therapy.

Von Willebrand disease (vWD), similar to hemophilia A, is a group of inherited bleeding disorders related to the absence or defects of von Willebrand factor, a clotting protein, needed to achieve hemostasis. Von Willebrand factor binds to factor VIII and platelets to generate a platelet plug during the clotting process. Unlike hemophilia A, vWD occurs equally in males and females. The disease leads to bleeding from impaired platelet adhesion and aggregation, which may be accompanied by reduced levels of factor VIII. Mucous membrane and skin bleeding symptoms, as well as bleeding with surgical or other hematostatic challenges, may occur in these patients. The prevalence of the disease is estimated to affect between 1 in 100 to 10,000 individuals. O'Brien, et al in 2003 and James, et al in 2007 noted that the incidence of vWD mutations was higher in patients with type O blood. Pregnancy can increase vWF levels and make diagnosis difficult. There are 3 major subtypes of vWD identified. Type 1 is a partial quantitative deficiency of vWF deficiency and accounts for 75% of all patients. Type 2

is a more pronounced qualitative deficiency and comprises almost all the remaining 25% of patients. Type 3 is characterized as a complete vWF deficiency and occurs very rarely. Type 2 disease is further divided into 4 variants named 2A, 2B, 2M, 2N on the basis of identified phenotypes. For type 3 vWD patients, their inherent factor VIII levels are typically very low. Acquired von Willebrand syndrome may also occur, but is highly rare, occurring in fewer than 1 in 100,000 adults. Three main approaches for the treatment of vWD are used and include increasing plasma concentrations of vWF through stimulation with desmopressin (DDAVP); replacing vWF by using human plasma-derived viral inactivated concentrates; and promoting hemostasis by utilizing hemostatic agents with mechanisms other than increasing vWF. Regular prophylaxis for von Willebrand patients is seldom required.

## PHARMACOLOGY[53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88]

Factor VIII and IX, along with factor VII-containing products, are intravenously administered and designed to supplement endogenous coagulation factors in patients with hemophilia A and B.

Products are differentiated based upon factor type, whether they are derived from pooled human plasma in the manufacturing process, as well as their level of purity or purification process.

Among hemophilia A or factor VIII products, those produced by cloning of the factor VIII gene, or the recombinant process, include Advate, Adynovate, Afstyla, Eloctate, Esperoct, Kovaltry, Novoeight, Nuwiq, Obizur, Jivi, Kogenate FS, Recombinate, and Xyntha. Kogenate FS is manufactured by Bayer Corporation who markets the recombinant factor VIII product as Kogenate FS. Since Recombinate has been found to contain animal and/or human plasma-derived proteins in the cell culture medium, as well as in the final product formulation, they are considered first generation products. Kogenate FS and Obizur, second generation recombinant products, are considered an advance over first generation products as they contain animal or human plasma in the medium but not in the final formulation vial. Adynovate, Advate, Afstyla, Eloctate, Esperoct, Jivi, Kovaltry, Novoeight, Nuwiq, and Xyntha are considered third generation factor VIII products due to the fact that they do not contain any animal or human plasma-derived proteins in either the culture medium or final formulation. Esperoct is a glycopegylated form of recombinant anti-hemophilic factor, in which the factor VIII is conjugated to a polyethylene glycol (PEG) molecule thereby increasing the half-life and decreasing the clearance compared to the non-pegylated molecule. Xyntha is a B-domain deleted product that has the B-domain deleted from the factor VIII gene prior to its insertion into Chinese hamster ovary cells. There is no known functional impact or role for the B-domain on factor VIII activity and its removal simply serves to increase the manufacturing output without affecting the resultant product's biological activity.

In 2014, Obizur was introduced as the only factor VIII product indicated for the treatment of acquired hemophilia A. In acquired hemophilia A, patients develop autoantibodies to their normal factor VIII genes neutralizing circulating human factor VIII, thereby creating a functional factor deficiency. Obizur is a recombinant analogue of porcine factor VIII. Once activated in the body, the porcine factor VIII demonstrates comparable activity to normal endogenous human activated factor VIII.

Pooled human plasma-derived factor VIII products for the treatment of hemophilia A include Alphanate, Hemofil M, Humate-P, and Koate-DVI. Wilate is a plasma-derived product only indicated for use in patients with vWD. Although Wilate is not indicated in hemophilia A, it does contain factor VIII. The ratio of vW factor to factor VIII for Wilate is 1:1. Alphanate and Humate-P also carry an indication for treatment of vWD patients and their ratios of vW factor to factor VIII are 1.3:1 and 1.8-2.4:1,

respectively. While these products may be used to treat vWD patients, they are not identical and should not be regarded as interchangeable. Vonvendi is a new recombinant von Willebrand factor product also for use only in vWD patients.

In late 2017, Hemlibra entered the market as the first monoclonal antibody agent for use in adult and pediatric hemophilia A patients with inhibitors to factor VIII. Hemlibra, (emicizumab-kxwh), is a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody. In 2018, its approval was expanded and now includes patients with hemophilia A with or without inhibitors. Hemlibra possesses a bispecific antibody structure binding to both factor IXa and factor X. Hemlibra acts to bridge activated factor IX and factor X, restoring the function of missing activated factor VIII required for effective hemostasis. Since Hemlibra has no structural relationship or sequence homology to factor VIII, it does induce or enhance the development of direct factor VIII inhibitors.

When considering factor IX products for the treatment of hemophilia B, Alprolix, BeneFIX, Idelvion, Ixinity, Rebinyn, and Rixubis are products made by recombinant technology; all other products are derived from human plasma. Additionally, the manufacturing process for these 6 products does not use any human or animal proteins making the risk of human blood-borne viral contamination extremely low. AlphaNine SD and Mononine are human plasma-derived products that are considered to be of high purity in comparison to other plasma-derived factor IX agents, employing added and improved methods of screening and viral depletion. While these additional methods serve to reduce the risk, there does remain the slight possibility of viral transmission. Transmission of human parvovirus B19 and hepatitis A have occurred; however, the risk has been reduced with the use of additional viral attenuation methods, such as ultrafiltration. Profilnine SD is also human plasma-derived products considered to be of lower purity. It is also referred to as Prothrombin Complex Concentrates (PCCs) as it contains detectable levels of other clotting factors including factors II, VII, IX, and X. Profilnine SD can, in some instances, be used to treat patients with deficiencies of factors II and X off-label, but it can vary significantly in the amount of factors that it contains. Further complicating the additional use is the fact that there commonly may be marked differences in factor content between different lots of the same agent produced by the same manufacturer.

In mid-2014, 2 new FC fusion protein factor products were introduced to the market; Eloctate (a recombinant factor VIII product) and Alprolix (a recombinant factor IX product). In 2016, a pegylated version, Adynovate (a recombinant factor VIII product), was also introduced to the market. In 2018, a second pegylated product, Jivi, was approved and entered the market. The theory behind the FC protein, as well as the PEGylated product, is to prolong the half-life of the coagulation factor in clinical use, thereby potentially increasing the interval of administration in prophylactic dosing regimens. Neither the fusion protein concept nor the pegylation process increases the potency of the factor in correcting bleeds; they are only intended to attempt to prolong the half-life. While clinical trials did indicate the half-life of the fusion protein may be increased in adults, the pharmacologic variability in pediatric hemophilia patients made any prolongation less certain. With pegylation, there is a reduction of binding to the factor VIII clearance receptor (LRP1). Clinical trials demonstrated a median reduction in dosing frequency of 33.7% (approximately 1 day) between doses. Manufacturer recommendations deferred to individual patient response and physician evaluation (see *Dosages* section).

In 2016, Afstyla (a recombinant single-chain factor VIII) entered the market. The physiochemical properties of the single-chain formulation are anticipated to extend the half-life of the product *in vivo*, potentially reducing the frequency of dosing. Clinical trials of the single-chain product appear to

parallel the FC protein products, increasing the median half-life in adults and, to a lesser degree, in children. Again, manufacturer recommendations emphasize that patient response and individual characteristics be taken into account by the prescriber to determine optimal dosing frequency.

In 2016, Idelvion (a recombinant albumin fusion protein factor IX product) was introduced. Similar to the FC fusion protein concept, the albumin fusion is intended to extend the half-life and decrease the frequency of either repeat dosing in on-demand situations or the frequency in prophylactic factor IX therapy. As with the other extended half-life products, the benefit is noted more in adults and adolescents over the age of 12 than is seen in younger children. The final decision on dosing frequency is up to the physician based on patient parameters and clinical response.

In 2017, Rebinyn, a recombinant glycopegylated factor IX product, was approved. The rationale for pegylation is to prolong the half-life of the coagulation factor during clinical use. This was demonstrated in clinical trials; however, Rebinyn does not carry an indication as an extended half-life product or for use as routine prophylaxis therapy.

## PHARMACOKINETICS[89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124]

The pharmacokinetics of various factor products dosed on an episodic or prophylactic basis is generally stable; however, this can vary depending on individual patient characteristics and factors, such as the presence of inhibitors. In children, particularly those under the age of 12 years, more frequent and higher doses may be required due to increased clearance of products in this group.

The absolute bioavailability of Hemlibra (emicizumab-kxwh) was reported between 80.4% and 93.1% when administered subcutaneously into the abdomen, upper arm, or thigh. The mean elimination half-life is 26.9 days. The pharmacokinetics are not affected by patient age, race, inhibitor status, or mild to moderate hepatic or renal impairment. However, the predicted concentration in patients younger than 6 months were reported 19% to 33% lower than older patients. Weight-based dosing allows for similar drug exposure across body weight ranges.

## CONTRAINDICATIONS/WARNINGS[125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160]

Contraindications for factor products are similar. All the factor agents are contraindicated in patients who have known anaphylactic or severe hypersensitivity reactions to the components of each product or in patients who are known to have a normal coagulation mechanism. Preliminary indications of allergic reactions, which may escalate to anaphylaxis, can include angioedema, chest tightness, hypotension, rash, nausea, vomiting, paresthesia, restlessness, wheezing, and dyspnea. Should any of these symptoms occur, use of the factor product should be discontinued and appropriate treatment administered.

A potential for a clinical immune response associated with IgM anti-PEG antibodies is possible with the use of pegylated products. This effect may be manifested as symptoms of acute hypersensitivity and/or loss of drug effect, has been observed more frequently in younger patients. The symptoms of the clinical immune response are typically transient, however if symptoms persist a change to a previously effective factor product is advised.

Factor VIII products are contraindicated in patients who do not have hemophilia A or von Willebrand disease.

Factor IX products are contraindicated in patients who do not have hemophilia B.

Factor IX products have been associated with the development of thromboembolic complications, particularly when administered as a continuous infusion through a central venous catheter.

Feiba is contraindicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to coagulation factor VIII or coagulation factor IX. It is also contraindicated in patients with significant signs of disseminated intravascular coagulation (DIC) or in patients with acute thrombosis or embolism (including myocardial infarction). Feiba should be used with caution for breakthrough bleeding in patients receiving Hemlibra as cases of thrombotic microangiopathy (TMA) occurred in a clinical study. Feiba is known to contain blood group isohemagglutinins (anti-A and anti-B), which may interfere with some serological tests for red cell antibodies, such as antiglobulin test (Coombs test), following use.

Similarly, the warnings for all factor products are nearly equivalent. Initial treatment with all bleeding factor products should be performed under the supervision of a qualified healthcare professional experienced in the treatment of bleeding disorders. Recommended monitoring of plasma factor activity levels following administration of factor products is by 1-stage clotting assay or a chromogenic substrate assay to confirm that adequate levels have been achieved and maintained, when clinically indicated.

Hemlibra carries a boxed warning for the potential development of thrombotic microangiopathy (TMA) and thromboembolism. Cases were reported during clinical trials when patients received a cumulative amount of activated prothrombin complex concentrate (aPCC) averaging greater than 100 U/kg in a 24-hour period while patients were receiving prophylactic Hemlibra therapy. In the course of Hemlibra clinical trials, TMA was reported in 0.8% of patients and in 8.1% of patients who received ≥ 1 dose of aPCC. In the HAVEN 1 study, following the data cutoff for the primary analysis, a case of TMA developed in 1 patient 5 days after the most recent Hemlibra dose and after 4 consecutive days of treatment with aPCC for rectal hemorrhage, which was recurrent and eventually resulted in the patient's death. Notably, the investigator assessed the patient and determined the TMA was resolving at the time of death.[161] Thrombotic events were also reported in the course of clinical trials of Hemlibra when patients again received aPCC in an average cumulative amount greater that 100 U/kg during a 24-hour timeframe for 24 hours or more of emicizumab-kxwh prophylaxis. Thrombotic events were reported in 0.5% of patients and in 5.4% of patients who received ≥ 1 dose of aPCC. None of the reported thrombotic events were significant enough to require anticoagulation therapy. Similar to the experience with TMA, improvement or resolution was seen within 1 month following discontinuation of aPCC. Patients and providers should consider the benefits and risks if aPCC must be used in patients receiving emicizumab-kxwh prophylaxis therapy.

Vonvendi and Wilate carry warnings of thromboembolic reactions, including disseminated intravascular coagulation (DIC), venous thrombosis, pulmonary embolism, and myocardial infarction, especially in those prone to thrombotic risk factors. Patients should be monitored for early signs and symptoms of potential thrombotic events. Additionally, hypersensitivity reactions, including anaphylaxis, may occur with these products. If anaphylactic signs or symptoms are noted, discontinue use and provide immediate supportive care.

The emergence of nephrotic syndrome has been reported following immune tolerance induction with factor IX products in hemophilia B patients with factor IX inhibitors and a history of allergic reactions to factor IX.

NovoSeven carries a boxed warning for thrombosis. Serious arterial and venous thrombotic events have been reported following the administration of NovoSeven RT. The risk appears greater in patients presenting with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, a crush injury, septicemia, or concomitant treatment with aPCCs/PCCs (activated or non-activated prothrombin complex concentrates), older individuals especially those with acquired hemophilia receiving concurrent hemostatic therapy, and uncontrolled post-partum hemorrhage due to circulating tissue factor (TF) or predisposing coagulopathy. The potential benefit of use in these patients should be strongly considered in light of the increased risk. Patients should be carefully monitored for any signs or symptoms indicating activation of the coagulation system or development of thrombosis.

## DRUG INTERACTIONS[162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197]

There are no known or reported drug interactions with factor VIII or factor IX products. In many cases, drug interaction studies were not performed for coagulation factor products.

No drug-drug interaction studies have been conducted with Hemlibra.

## ADVERSE EFFECTS[198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249]

All factor products, factor VIII-, factor IX-, and factor VII-containing products, derived from pooled human plasma, carry a risk of transmitting infectious diseases. These risks have been attenuated by various purification methods employed in their manufacture. In general, for all these products, the benefits of these products outweigh the risks.

The plasma-derived factor IX products may present a greater risk of disseminated intravascular coagulation (DIC) or thrombosis when administered at frequent or prolonged intervals. This may be more critical for the Prothrombin Complex Concentrate (PCCs), Profilnine SD, that contains significant amounts of activated factors VII, X, and prothrombin. While the risk may be increased with plasma-derived products, the recombinant factor IX products Alprolix, BeneFIX, Idelvion, Ixinity, Rebinyn, and Rixubis have also been associated with the risk of development of thromboembolic complications.

Severe allergic reactions may occur in up to 50% of hemophilia B patients who have inhibitors. These reactions may include anaphylaxis to factor IX administration; it is possible that reactions of this type could represent the first signs and symptoms of inhibitor development. It is recommended that all newly-diagnosed hemophilia B patients, and, in particular, patients who have a family history of factor inhibitors, as well as those patients with genetic defects predisposed to inhibitor development, should receive their initial doses and factor administration treatments in a clinic, hemophilia treatment center, or hospital setting with the resources to immediately treat severe allergic reactions. These precautions should persist throughout the first 10 to 20 infusion treatments with factor IX concentrates. It is possible that reactions can be delayed or occur later; however, in these cases, they may be less severe.

The most significant adverse event that may occur for hemophilia A or B patients is the development of inhibitors. For hemophiliacs, inhibitors are IgG antibodies that neutralize clotting factors administered to control bleeding episodes. With the development of products with a greater level of purification, the development of inhibitors to factor VIII or factor IX coagulation factors is recognized as the most severe treatment-related complication in hemophilia.

In situations where a patient who has previously responded positively to factor infusion therapy fails to respond clinically to clotting factors, the presence of inhibitors should be suspected and appropriate testing performed. In situations where inhibitors are present, the expected response, clinical effect, and half-life of the transfused clotting factor are severely compromised. There are no documented cases where inhibitor development was attributed to a change in the specific factor product used.

Inhibitors are more frequently encountered in persons with severe hemophilia in comparison to patients diagnosed with moderate or mild hemophilia regardless of phenotype. The overall lifetime risk for the development of inhibitors in patients identified with severe hemophilia A is in the range between 20% and 30%. The risk is significantly lower for patients diagnosed with mild to moderate hemophilia, falling between 5% to 10% over a lifetime. Finally, the prevalence of inhibitor development is much less frequent in hemophilia B than hemophilia A, occurring in less than 5% of affected individuals. Regardless of hemophilia phenotype, inhibitors render the treatment of bleeding episodes with replacement factor concentrates difficult. Patients receiving clotting factor therapy should be screened for the potential of inhibitor development.

In severe hemophilia A, the median age of inhibitor development is 3 years or less as seen in most developed countries. For those patients with moderate to mild hemophilia A, the median age of inhibitor development is closer to 30 years of age. Development in mild to moderate patients is often seen in following intensive factor VIII exposure as a result of surgery.

In patients with severe hemophilia, the presence of inhibitors does not change the site, frequency, or severity of bleeds. Conversely, in patients with moderate or mild hemophilia, the development of inhibitors may serve to neutralize endogenously synthesized factor VIII, effectively converting the patient's phenotype to severe hemophilia. Bleeding manifestations in moderate to mild hemophilia that are complicated by the development of an inhibitor are frequently reminiscent of those seen in patients with acquired hemophilia A occurring as a result of the presence of auto-antibodies to a patient's own factor VIII. In such cases, there is a greater predominance of mucocutaneous, urogenital, and gastrointestinal bleeding sites. As a result, the risk of severe complications or even death from bleeding may be greater in these patients.

The presence of an inhibitor and the level of inhibitor involvement (quantification of the titer) should be performed in a qualified laboratory, preferably using the Nijmegen-modified Bethesda assay method. When the patients are children, screening for inhibitors should be performed once every 5 exposure days up to 20 factor exposure days, then every 10 factor exposure days between 21 and 50 exposure days. Following the initial phase of testing, evaluations should be performed at least twice a year until 150 exposure days have occurred. When dealing with adults who have experienced more than 150 factor exposure days, a review should be performed approximately every 6 to 12 months. If there is an instance of failure to adequately respond to normal factor concentrate replacement dose in a patient who previously demonstrated a positive clinical response, this is an indication to assess for the emergence of an inhibitor.

Inhibitor measurement should also be done for all patients who have been intensively treated with factor therapy for more than 5 days' duration, within 4 weeks of their last infusion. Inhibitors should be assessed prior to surgery or if recovery assays are not as expected. Again, in any case where the clinical response to treatment of bleeding is sub-optimal in the post-operative period, an assessment should be performed.

There are 2 primary types of inhibitors identified based upon their measurement in Bethesda units (BU). Low responding inhibitors are defined as those presenting an inhibitor level that is persistently < 5 BU/mL, while high responding inhibitors are defined as those having a Bethesda level ≥ 5 BU/mL.

Although high responding inhibitors tend to be persistent, if the patient does not undergo factor infusion therapy for a long period, the inhibitor titer levels may drop or even become undetectable. Unfortunately, this effect is only temporary and there will be a recurrence of an anamnestic response with a rise in the inhibitor titer level generally in 3 to 5 days following exposure to specific factor products. In contrast, certain low titer inhibitors may be transient and disappear commonly within 6 months of their initial detection and documentation. In these cases, this occurs despite any recent antigenic challenge with factor concentrates. In certain instances, very low titer inhibitors may not be detected by the Bethesda inhibitor assay, but are identified by a poor clinical response, sub-optimal recovery, and/or a shortened half-life for the agent utilized following clotting factor infusions.

As with all therapeutic proteins, there is a potential for immunogenicity with Hemlibra use. Detection of antibody formation is highly dependent on the sensitivity and specificity of the assay employed. The anti-Hemlibra antibody positive rate may be under-reported due to the limitation of the assay utilized. In April 2018 MASAC issued updated safety information for Hemlibra addressing the detection of anti-drug antibodies.[250] While no patients tested positive for an anti-drug antibody within the HAVEN 1 clinical trial, 1 pediatric patient within the ongoing HAVEN 2 clinical trial did develop an anti-drug antibody to Hemlibra that resulted in loss of efficacy. Anti-drug antibody to Hemlibra is distinct from the development of an inhibitor to factor VIII and anti-Hemlibra antibodies may alter efficacy, but will not affect the patient's underlying hemophilia or inhibitor status, nor the ability to manage bleeding events with conventional therapies, including bypassing agents.

## SPECIAL POPULATIONS[251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286]

### Pediatrics

Refer to the Food and Drug Administration (FDA)-approved indications table.

### Pregnancy

The factor VIII products Advate, Alphanate, Eloctate, Humate-P, Kogenate FS, Novoeight, Obizur, Recombinate, Wilate, and Xyntha all carry a pregnancy category designation C. Similarly, factor IX products AlphaNine SD, Alprolix, Ixinity, Mononine, Profilnine SD, and Rixubis also carry a pregnancy category C. Feiba and NovoSeven RT are also pregnancy category C. There are no data indicating safety of Adynovate, Afstyla, BeneFIX, Esperoct, Hemlibra, Hemofil M, Idelvion, Jivi, Kovaltry, Nuwiq, Rebinyn, and Vonvendi in pregnant women. These agents should only be used during pregnancy if clearly warranted.

## Geriatrics

Clinical studies of factor products and Hemlibra did not include subjects ≥ 65 years of age, or did not have sufficient patients to determine differences in response or efficacy. Dosing of factor products for elderly patients should be individualized.

## DOSAGES[287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332]

There are 2 primary methodologies employed in factor replacement therapy. Commonly, mild to moderate hemophilia A and B patients may be treated with episodic or "on demand" treatment of bleeds. Severe hemophilia patients, particularly younger hemophilia patients, are recommended to begin prophylactic factor replacement therapy where individualized dosages are given on a scheduled basis. The 2020 World Federation of Hemophilia (WFH) guidelines state the standard of care for all patients with severe hemophilia is prophylaxis with clotting factor concentrates (CFCs) or other hemostatic products for the prevention of bleeding; this is recommended to be initiated before 3 years of age to prevent musculoskeletal complications caused by recurrent joint or muscle bleeds. Furthermore, it is stated that episodic or "on demand" clotting factor replacement therapy is no longer considered a long-term treatment option.

General dosing information for hemophilia A is commonly included in the respective product labels. These recommendations are usually provided as a range or percentage based on factor VIII or factor IX activity in the blood. The percentages or range can vary for each individual due to a variety of reasons including hemorrhage types, different surgical procedures, the presence or absence of inhibitors, and acute treatment versus prophylactic therapy. To assure optimal treatment outcomes, it is recommended that factor activity levels be monitored during replacement therapy. Ultimately, dosing decisions should be under the direction of the physician treating the condition.

The 2016 National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) guidelines made recommendations regarding prophylaxis dosing (regular administration of clotting factor concentrate to prevent bleeding) for younger patients with hemophilia A or B. Because of the benefits demonstrated by prophylactic therapy, MASAC recommends that prophylaxis be considered optimal therapy for individuals with severe hemophilia A or B where endogenous factor levels are found to be less than 1%. Prophylaxis therapy should be initiated early, with the goal of keeping trough values for factor VIII or factor IX levels above 1% between doses, although benefit may still be seen when trough levels fall below the target goal. The optimal dosing and frequency of administration for each individual patient should be determined by appropriate laboratory monitoring. Protocols should be individualized to the extent possible taking into account age, bleeding phenotype, activity, cost, and factor availability. Individuals should have regular follow-up visits for evaluation of joint status, document bleeds that occur during prophylaxis, and to monitor for inhibitor development. There are no definitive guidelines for stopping prophylactic dosing and some individuals may require this modality for their entire life. The analysis of risks and benefit should be made by practitioners and family members following careful evaluation and discussion. The analysis should be evaluated periodically as new data emerges along with factor usage and any changes in bleeding patterns. Where applicable, prophylaxis dosing recommendations from manufacturers for specific factor products is summarized in the table below.

There are no specific guidelines regarding when or if prophylaxis should stop or at what age prophylaxis benefit decreases, although some data suggest that some young adults do well after prophylaxis has ended. Recombinant factor products are the most appropriate choice for prophylaxis because of markedly reduced risk of blood-borne infection; however, as noted earlier, there are data that suggest that plasma-derived factor VIII products may have a marginally-reduced risk although the conclusion is not definitive. Potential reasons to discontinue prophylaxis include development of an inhibitor or patient preference (with physician agreement).

## Manufacturer Recommended Prophylaxis Dosing

### *Factor VIII Products*

| Drug | Manufacturer Recommended Starting Doses for Prophylaxis |
|---|---|
| antihemophilic factor VIII – recombinant<br>(Advate) | For children and adults: 20 to 40 IU/kg every other day (3 to 4 times a week) or every third day to maintain factor VIII trough levels greater than or equal to 1%<br>Adjust dosing based on patient's clinical response |
| antihemophilic factor VIII – recombinant, PEGylated<br>(Adynovate) | For adults and adolescents (≥ 12 years): 40 to 50 IU/kg 2 times a week<br>For children < 12 years: start with 55 IU/kg 2 times a week with maximum of 70 IU/kg<br>Adjust dosing based on patient's clinical response |
| antihemophilic factor VIII – recombinant, single chain<br>(Afstyla) | For children < 12 years: 30 to 50 IU/kg 2 to 3 times a week<br>For adults and adolescents ≥ 12 years: 20 to 50 IU/kg 2 to 3 times a week<br>Adjust dosing based on patient's clinical response |
| antihemophilic factor VIII – plasma derived<br>(Alphanate) | Dose (units) = body weight (kg) x desired FVIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)<br>The dosing frequency should be determined by the type of bleeding episode and the recommendation of the physician |
| antihemophilic factor VIII – recombinant, FC fusion protein<br>(Eloctate) | For children and adults: 50 IU/kg every 4 days<br>Adjust dosing based upon patient's clinical response<br>Dosing range based upon response may be adjusted within 25 to 65 IU/kg every 3 to 5 days<br>Doses of up to 80 IU/kg with greater frequency may be required for children < 6 years of age |
| antihemophilic factor – recombinant, glycopegylated-exei<br>(Esperoct) | For children < 12 years: 65 IU/kg twice weekly<br>For adults and adolescents ≥ 12 years: 50 IU/kg every 4 days<br>Dosing frequency may be adjusted based on an individual's bleeding episodes; can also be dosed to achieve a specific target FVIII activity level using a formula that considers a patient's body weight and desired FVIII increase |
| antihemophilic factor VIII – plasma derived<br>(Hemofil M) | N/A |
| antihemophilic factor VIII – plasma derived<br>(Humate-P) | N/A |
| antihemophilic factor VIII – recombinant, PEGylated<br>(Jivi) | For adults and adolescents ≥ 12 years: 30 to 40 IU/kg 2 times a week<br>Based on bleeding episodes, regimen may be adjusted to 45 to 60 IU/kg every 5 days<br>Adjust dosing and frequency based on patient's clinical response |
| antihemophilic factor VIII – plasma derived<br>(Koate DVI) | N/A |

### *Factor VIII Products (continued)*

| Drug | Manufacturer Recommended Starting Doses for Prophylaxis |
|---|---|
| | |
| antihemophilic factor VIII – recombinant (Kogenate FS) | For children: 25 IU/kg every other day<br>For adults: 25 IU/kg 3 times a week |
| antihemophilic factor VIII – recombinant (Kovaltry) | For children < 12 years: 25 to 50 IU/kg 2 to 3 times a week or every other day based on individual requirements<br>For adults and adolescents ≥ 12 years: 20 to 40 IU/kg 2 to 3 times a week<br>Adjust dosing based on patient's clinical response |
| antihemophilic factor VIII – recombinant (Novoeight) | For children < 12 years of age: 20 to 50 IU/kg every other day or 20 to 60 IU/kg 3 times a week<br>For adults and children ≥ 12 years: 20 to 40 IU/kg every other day or 20 to 50 IU/kg 3 times a week<br>Adjust dosing based on patient's clinical response |
| antihemophilic factor VIII – recombinant (Nuwiq) | For children < 12 years of age: 30 to 50 IU/kg every other day or 3 times a week<br>For adults and children ≥ 12 years: 30 to 40 IU/kg every other day<br>Adjust dosing based on patient's clinical response |
| antihemophilic factor VIII – recombinant, porcine sequence (Obizur) | N/A |
| antihemophilic factor VIII – recombinant (Recombinate) | N/A |
| antihemophilic factor VIII – recombinant (Xyntha) | For adults and adolescents ≥ 12 years: 30 IU/kg administered 3 times weekly<br>For children < 12 years: 25 IU/kg every other day<br>More frequent or higher doses may be needed in children < 12 years due to the higher clearance in this patient population<br>For all patients, adjust the dose or frequency based on the patient's response |

### *Factor IX Products*

| Drug | Manufacturer Recommended Starting Doses for Prophylaxis |
|---|---|
| coagulation factor IX – plasma derived (AlphaNine SD) | N/A |
| coagulation factor IX – recombinant, FC fusion protein (Alprolix) | For children and adults: 50 IU/kg once a week or 100 IU/kg once every 10 days<br>Adjust dosing based upon patient's clinical response |
| coagulation factor IX – recombinant (BeneFIX) | For children and adults: 100 IU/kg once weekly<br>Patients < 12 years have lower recovery, shorter half-life, and higher clearance (based on per kg body weight) as compared to adolescents and adults<br>The dosing regimen (dose or frequency) should be adjusted based on the patient's clinical response |

### *Factor IX Products (continued)*

| Drug | Manufacturer Recommended Starting Doses for Prophylaxis |
|---|---|
| coagulation factor IX – recombinant, albumin fusion protein (Idelvion) | For children < 12 years of age: 40 to 55 IU/kg every 7 days<br>For adults and children ≥ 12 years: 25 to 40 IU/kg every 7 days; if well controlled, may switch to 50 to 75 IU/kg every 14 days<br>Adjust dosing based on patient's clinical response |
| coagulation factor IX – recombinant (Ixinity) | N/A |
| coagulation factor IX – plasma derived (Mononine) | N/A |
| coagulation factor IX – plasma derived (Profilnine SD) | N/A |
| coagulation factor IX – recombinant, Pegylated (Rebinyn) | N/A |
| coagulation factor IX – recombinant (Rixubis) | For patients < 12 years of age previously treated with factor IX: 60 to 80 IU/kg twice a week<br>For patients ≥ 12 years previously treated with factor IX: 40 to 60 IU/kg twice a week<br>Adjust dosing based upon patient's clinical response |

### *Factor VIIa and Activated Prothrombin Complex Concentrate Products*

| Drug | Manufacturer Recommended Starting Doses for Prophylaxis |
|---|---|
| anti-inhibitor coagulant complex plasma derived (Feiba) | 85 IU/kg every other day<br>Adjust dosing based on patient's clinical response<br>Not to exceed a single dose of 100 units/kg of body weight or a total daily dose of 200 units/kg body weight |
| coagulation factor VIIa – recombinant (NovoSeven RT) | N/A |

### *Factor IXa and Factor X Directed Antibody Products*

| Drug | Manufacturer Recommended Starting Doses for Prophylaxis |
|---|---|
| emicizumab-kxwh (Hemlibra) | 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by a maintenance dose; the maintenance dose can be 1.5 mg/kg once weekly, 3 mg/kg once every 2 weeks, or 6 mg/kg once every 4 weeks; the maintenance regimen should be based on healthcare provider preference and patient adherence<br>Prophylactic use of bypassing agents should be discontinued 1 day prior to starting emicizumab-kxwh; prophylactic use of factor VIII product may continue during first week of emicizumab-kxwh prophylaxis |

### *Factor X and Factor XIII Products*

| Drug | Manufacturer Recommended Starting Doses for Prophylaxis |
|---|---|
| coagulation factor X - plasma derived<br>(Coagadex) | Age ≥ 12 years: 25 IU/kg twice weekly<br>Age < 12 years: 40 IU/kg twice weekly<br>Adjust dosage regimen to clinical response and trough levels of Factor X of at least 5 IU/dL. Do not exceed a peak level of 120 IU/dL |
| coagulation factor XIII – plasma derived<br>(Corifact) | 40 IU/kg body weight infused IV at a rate not to exceed 4 mL/min; adjust dose as described in the product labeling to maintain 5% to 20% trough level of FXIII activity<br>Administer every 28 days for routine prophylaxis<br>For peri-operative management of surgical bleeding, dosage is individualized based on patient's FXIII activity level, type of surgery, and clinical response; dosage adjustments are described in the product labeling |
| coagulation factor XIII A-subunit– recombinant<br>(Tretten) | 35 IU/kg once monthly to achieve a target trough level of FXIII activity ≥ 10% using a validated assay;<br>A dose adjustment may be considered to achieve adequate coverage; however, a dose of 35 IU/kg is sufficient to replace 100% of FXIII activity, and higher doses may not increase the levels of tetrameric Factor XIII |

### *von Willebrand Products*

| Drug | Manufacturer Recommended Starting Doses for Prophylaxis |
|---|---|
| von Willebrand factor – recombinant<br>(Vonvendi) | N/A |
| von Willebrand factor/coagulation factor VIII complex – plasma derived<br>(Wilate)* | For adults and adolescents ≥ 12 years: 20 to 40 IU/kg every 2 to 3 days<br>Dosing should be defined by the patient's clinical status and response |

*Routine prophylaxis dosing is for patients with hemophilia A; for vWD, it is indicated for On-demand treatment and perioperative management

Episodic dosing is also often based on physician preference considering the patient's severity, location, and type of trauma. The goal of episodic treatment is to raise the factor level in the blood from 40% to 100% depending on the location and level of injury. These calculations include the patient's current weight, the factor level to be reached, and a constant depending on whether the patient had hemophilia A or B. Factor VIIa and activated PCC Products, commonly referred to as by-passing agents have unique dosing recommendations for the treatment of bleeding episodes in hemophilia A & B with inhibitors as well as other indicated uses. Providers should refer to the individual drugs prescribing recommendations and adjust dosage until hemostasis is achieved. As previously stated, final dosing decisions should be under the direction of the physician treating the condition and consider patient and product specifics.

For hemophilia A patients, a commonly accepted calculation is: patient weight in pounds divided by 4.4 multiplied by the factor level or correction factor desired. The result is the number of factor VIII units required:

Weight in pounds ÷ 4.4 × factor level desired = factor VIII units required

or

body weight (kg) × desired factor VIII increase (IU/dL or % normal) × 0.5 (IU/kg per IU/dL)

Patients' pharmacokinetics may vary. Base dose and frequency on individual clinical response, including appropriate laboratory tests (e.g., serial factor VIII activity assays) as indicated in the product labeling.

For factor X products, estimate the expected *in vivo* peak increase in factor X level expressed as IU/dL (or % of normal) using the following formula:

For patients ≥ 12 years of age:

Estimated increment of factor X (IU/dL or % of normal) = [Total dose (IU)/body weight (kg)] x 2

For patients < 12 years of age:

Estimated increment of factor X (IU/dL or % of normal) = [Total dose (IU)/body weight (kg)] x 1.7

Calculate the dose to achieve a desired *in vivo* peak increase in Factor X level using the following formula:

For patient ≥ 12 years of age:

Dose (IU) = body weight (kg) x desired factor X rise (IU/dL or % of normal) x 0.5

For patients < 12 years of age:

Dose (IU) = Body weight (kg) x desired factor X rise (IU/dL) x 0.6

For hemophilia B patients, a similar commonly accepted calculation is: patient weight in pounds divided by 2.2 multiplied by the factor level or correction factor desired. The result is the number of factor IX units required:

Weight in pounds ÷ 2.2 × factor level desired = factor IX units required

In general, every attempt should be made to match the vial strength to the final correction required. It is permissible for hemophilia A patients to receive a bit more factor than the maximum calculated dose; however, hemophilia B patients should be cautioned not to exceed the maximum units required.[333] Depending on severity, if bleeding persists beyond 24 hours, the physician should be consulted and additional doses may be required.

One of the most complex and problematic aspects of treating hemophilia patients is the development of inhibitors, IgG antibodies, which neutralize exogenous clotting factors. If a patient does not respond clinically to the usual dose of factor which has previously been responsive, the development of an inhibitor must be suspected as these may be considered the most severe treatment-related complication in hemophilia. In these cases, care must be coordinated with the expertise of a hematologist who specializes in bleeding disorders, as well as a hemophilia treatment center. The 2020 WFH guidelines state that systematic surveillance for inhibitors as well as comprehensive management of inhibitors should be initiated for hemophilia A patients, especially when patients are at the highest

risk during their first 20 exposures to CFCs (1 exposure is defined as all CFCs administered during a 24-hour period), and thereafter up to 75 exposures.

There are 3 primary methodologies for the treatment of persons with inhibitors including: High-Dose Clotting Factor Concentrates; Bypassing Agents; and Immune Tolerance Induction Therapy. Bypassing Agents are special blood products used to treat bleeding in people with high titer inhibitors. They are called "bypassing agents" since, instead of replacing the missing factor, they go around (or bypass) the factors that are blocked by the inhibitor to help the body form a normal clot. People taking bypassing agents should be monitored closely to make sure the blood is not clotting too much or clotting in the wrong place in the body; and Immune Tolerance Induction (ITI) Therapy: The goal of ITI therapy is to reduce/eliminate the inhibitor reaction from the blood and to teach the body to accept clotting factor concentrate treatments. With ITI therapy, people receive large amounts of clotting factor concentrates every day or every other day for many weeks or months.

The 2020 WFH guidelines state that inhibitor eradication is currently best achieved through ITI therapy. ITI therapy requires specialized medical expertise, is costly, and may take a long time to work. In many cases, ITI gets rid of the inhibitor. However, patients may need to continue taking frequent, large amounts of factor concentrates for many years to keep the inhibitor from coming back.

The choice of a specific product in treating persons with inhibitors involves consideration of the titer of the inhibitor, clinical response to product, site, and nature of bleed. Inhibitor activity is measured in Bethesda units (BU). Patients who have a confirmed low-responding inhibitor (<5 BU/mL) may be treated with factor replacement at a much higher dose than normal. This increased dosing serves, if possible, to neutralize the inhibitor with excess factor activity and stop and active bleeding. Also known as High-Dose Clotting Factor Concentrate, it is important to test the blood and measure the factor level after this new treatment schedule is established to see if the inhibitor is gone.

Patients with a documented high responding inhibitor (≥ 5 BU/mL), but who have low titers, may be treated in a similar manner in emergency situations until an anamnestic response occurs. This usually occurs in 3 to 5 days, with the goal of eliminating additional treatment with concentrates that only contain the missing factor.

Patients who have a Bethesda assay inhibitor level ≥ 5 BU are unlikely to show an effective clinical response to factor replacement designed to overwhelm the inhibitor without continuous infusion therapy at ultra-high doses. In these instances, the use of alternative bypassing agents, such as a factor VIIa containing product (NovoSeven RT) or, in some cases, prothrombin complex concentrates (PCC), including the activated forms (aPCC - Feiba), may prove more successful. It has been shown that efficacy of 2 doses of factor VIIa and 1 dose of aPCC for management of joint bleeding are essentially equivalent. As with all factor therapy, however, some patients may respond better to 1 agent than the other, underscoring the importance of individualized therapy.

One additional therapy available for patients with severe hemophilia A is the potential eradication of inhibitors via Immune Tolerance Induction (ITI) therapy. One primary issue is that, prior to the initiation of ITI therapy, high-responding patients diagnosed with high-responding inhibitors should avoid the use of any factor VIII products so inhibitor titers may fall in the hope of avoiding a persistent anamnestic rise. To date, no optimal regimen for ITI, either through product selection or dose requirements, has been defined or achieved a consensus. An international trial comparing the dosage of 50 IU/kg 3 times a week to 200 IU/kg daily was recently stopped due to safety concerns although interpretation of the data collected is an ongoing process.

Overall, the response to ITI may be less favorable in patients with moderate/mild hemophilia and current experience with ITI for hemophilia B inhibitor patients is limited. The principles for treatment of hemophilia B inhibitor patients is similar, but rate of success has proven is much lower. There is a possibility of the development of nephrotic syndrome by hemophilia B patients who have a documented history of severe allergic reactions to factor IX and undertake ITI therapy. The resultant nephrotic syndrome is not always reversible upon cessation of the ITI therapy. Alternative treatment schedules, which include the addition of immunosuppressive therapies, are reported to have been successful.

While there has been interest in the use of immunosuppressive therapies for hemophilia patients with inhibitors, their role is not yet defined. At present, there is no consensus whether they have a place in the management of these patients.

## Product Storage and Availability

### *Factor VIII Products*

| Drug | Purification | Storage | Availability |
|---|---|---|---|
| antihemophilic factor VIII – recombinant (Advate) | Immunoaffinity chromatography (IC) and solvent/detergent (SD) | Up to 6 months but the temperature should not to exceed 30°C (86°F) – do not freeze; the powder form should be refrigerated | Single-dose vials of 250 IU, 500 IU, 1,000 IU, 1,500 IU, 2,000 IU, 3,000 IU, and 4,000 IU |
| antihemophilic factor VIII – recombinant, PEGylated (Adynovate) | Immunoaffinity chromatography (IC) and solvent/detergent (SD) | At +2°C to +8°C (36°F to 46°F) – do not freeze; may be stored at room temperature not exceeding 30°C (86°F) up to 3 months not past expiration date; do not return room temperature stored product to refrigerator; protect from extreme light | Single-dose vials of 250 IU, 500 IU, 750 IU, 1,000 IU, 1,500 IU, 2,000 IU, and 3,000 IU |
| antihemophilic factor VIII – recombinant, single chain (Afstyla) | Solvent detergent (SD) and nanofiltration | At +2°C to +8°C (36°F to 46°F) – do not freeze; may be stored at room temperature not exceeding 25°C (77°F) up to 3 months not past expiration date; do not return room temperature stored product to refrigerator and discard vials; protect from light | Single-dose vials of 250 IU, 500 IU, 1,000 IU, 1,500 IU, 2,000 IU, 2,500 IU, and 3,000 IU |
| antihemophilic factor VIII – plasma derived (Alphanate) | Affinity chromatography (AC), solvent/detergent (SD), and dry heat 72 hours at 80°C | Up to the expiration date as long as storage temperature does not exceed 25°C (77°F) – do not freeze | Single-dose vials in strengths of 250 IU, 500 IU, 1,000 IU, 1,500 IU, and 2,000 IU |
| antihemophilic factor VIII – recombinant, FC fusion protein (Eloctate) | Solvent/detergent (SD) and nanofiltration | Store between 2°C to 8°C – do not freeze; may store at room temperature not to exceed 30°C (86°F) for up to 6 months; following storage at room temperature, do not refrigerate again | Single-use vials of 250 IU, 500 IU, 750 IU, 1,000 IU, 1,500 IU, 2,000 IU, 3,000 IU, 4,000 IU, 5,000 IU, and 6,000 IU with diluent |

***Factor VIII Products (continued)***

| Drug | Purification | Storage | Availability |
|---|---|---|---|
| antihemophilic factor – recombinant, glycopegylated-exei (Esperoct) | detergent (Triton X-100) and 20-nm filtration | In the powder form at +2°C to +8°C (36°F to 46°F) for up to 30 months from the date of manufacture until the expiration date; within the 30-month period, may be kept at room temperature up to 30°C (86°F) for a period of up to 12 months, or up to 40°C (104°F) for up to 3 months, do not refrigerate again – do not freeze; protect from light | Single-dose glass vials in strengths of 500 IU, 1,000 IU, 1,500 IU, 2,000 IU, and 3,000 IU |
| antihemophilic factor VIII – plasma derived (Hemofil M) | Immunoaffinity chromatography (IC), solvent/detergent (SD) and nanofiltration | Based upon the bottle expiration date but the temperature should not exceed 30°C (86°F) – do not freeze | Single-dose bottles in strengths of 250 IU, 500 IU, 1,000 IU, and 1,700 IU |
| antihemophilic factor VIII – plasma derived (Humate-P) | Pasteurization 10 hours at 60°C | Up to 36 months or the expiration date on the bottle but the temperature should not exceed 25°C (77°F) – do not freeze | Single-dose vials in strengths of 250 IU, 500 IU, and 1,000 IU of factor VIII/vial and 600 IU, 1,200 IU, and 2,400 IU vWF:RCo/vial |
| antihemophilic factor VIII – recombinant, PEGylated (Jivi) | Anion-exchange chromatography and ultrafiltration | At +2°C to +8°C (36°F to 46°F) for up to 24 months from manufacture date; within the 24-month period, may be stored for a period of up to 6 months at up to +25°C or 77°F; following storage at room temperature, do not refrigerate again – do not freeze, protect from extreme light | Single-use glass vials in strengths of 500 IU, 1,000 IU, 2,000 IU, and 3,000 IU |
| antihemophilic factor VIII – plasma derived (Koate DVI) | Solvent/detergent (SD) and dry heat 72 hours at 80°C | Up to 6 months but the temperature should not exceed 25°C (77°F) – do not freeze | Single-dose bottles in strengths of 250 IU, 500 IU, and 1,000 IU |
| antihemophilic factor VIII – recombinant (Kogenate FS) | Immunoaffinity chromatography (IC) and solvent/detergent (SD) | At +2°C to +8°C (36°F to 46°F) for up to 30 months from manufacture date; within the 30-month period, may be stored for a period of up to 12 months at up to +25°C or 77°F – do not freeze; protect from extreme light | Single-use glass vials in strengths of 250 IU, 500 IU, 1,000 IU, 2,000 IU, and 3,000 IU |
| antihemophilic factor VIII – recombinant (Kovaltry) | Solvent/detergent (SD) and nanofiltration | At +2°C to +8°C (36°F to 46°F) – do not freeze; may be stored at room temperature not exceeding 25°C (77°F) up to 30 months from date of manufacture; do not return room temperature stored product to refrigerator and discard vials; protect from extreme light | Single-use glass vials and kits containing Kovaltry vials and Bio-Set® reconstitution system in strengths of 250 IU, 500 IU, 1,000 IU, 2,000 IU, and 3,000 IU |

***Factor VIII Products (continued)***

| Drug | Purification | Storage | Availability |
|---|---|---|---|
| antihemophilic factor VIII – recombinant<br>(Novoeight) | Immunoaffinity chromatography (AC), solvent/detergent (SD), anion-exchange chromatography, gel filtration and nanofiltration | At +2°C to +8°C (36°F to 46°F) for up to 30 months from manufacture date; within the 30-month period, may be stored for a period of up to 12 months at up to +30°C or 86°F; following storage at room temperature, do not refrigerate again; do not use after the end of the 12-month period at room temperature storage, or after the expiration date stated on the vial, whichever occurs earlier; do not freeze | Single-use glass vials in strengths of 250 IU, 500 IU, 1,000 IU, 1,500 IU, 2,000 IU, and 3,000 IU |
| antihemophilic factor VIII Recombinant<br>(Nuwiq) | Chromatography, solvent/detergent (SD) and nanofiltration | Up to 24 months at +2°C to +8°C (36°F to 46°F) in the original containers to protect from light; may be stored for a period of up to 3 months at room temperature; once stored at room temperature, do not return to the refrigerator; do not freeze | Single-use vials in strengths of 250 IU, 500 IU, 1,000 IU, 2,000 IU, 2,500 IU, 3,000 IU, and 4,000 IU |
| antihemophilic factor VIII – recombinant, porcine sequence<br>(Obizur) | Chromatography, solvent/detergent (SD) and nanofiltration | At +2°C to +8°C (36°F to 46°F) up to expiration date – do not freeze | Single-dose vials in strengths of 500 U |
| antihemophilic factor VIII – recombinant<br>(Recombinate) | Immunoaffinity chromatography (IC)<br>solvent/detergent (SD) | Based upon the bottle expiration date, but the temperature should not exceed 30°C (86°F) – do not freeze | Single-dose vials in the following strengths: 220 to 400 IU; 401 to 800 IU; 801 to 1,240 IU; 1,241 to 1,800 IU; and 1,801 IU to 2,400 IU |
| antihemophilic factor VIII – recombinant<br>(Xyntha) | Affinity chromatography (AC)<br>solvent/detergent (SD) and nanofiltration | Up to 36 months at +2°C to +8°C (36°F to 46°F) until expiration date<br>Up to 3 months but the temperature should not exceed 25°C (77°F), may be returned to refrigerator until expiration – do not freeze | Single-use vials and prefilled dual-chamber syringes (Solofuse) in strengths of 250 IU, 500 IU, 1,000 IU, 2,000 IU, and 3,000 IU (Solofuse only) |

### *Factor IX Products*

| Drug | Purification | Storage | Availability |
|---|---|---|---|
| coagulation factor IX – plasma derived (AlphaNine SD) | Dual affinity chromatography (AC), solvent/detergent (SD), and nanofiltration | Up to 3 years or expiration date if stored between 2°C to 8°C – do not freeze; may store at room temperature not to exceed 30°C (86°F) for up to 1 month | Single-dose vials of 500 IU, 1,000 IU, and 1,500 IU with diluent |
| coagulation factor IX – recombinant, FC fusion protein (Alprolix) | Column chromatography and nanofiltration | Store between 2°C to 8°C – do not freeze; may store at room temperature not to exceed 30°C (86°F) for up to 6 months; following storage at room temperature, do not refrigerate again; protect from light | Single-use vials of 250 IU, 500 IU, 1,000 IU, 2,000 IU, 3,000 IU, and 4,000 IU with diluent |
| coagulation factor IX – recombinant (BeneFIX) | Affinity chromatography (AC) and viral filtration | Store between 2°C to 8°C; may store at room temperature not to exceed 30°C (86°F) – do not freeze | Single-use vials contain 250 IU, 500 IU, 1,000 IU, 2,000 IU, and 3,000 IU with diluent |
| coagulation factor IX – recombinant, albumin fusion protein (Idelvion) | Solvent/detergent (SD) and nanofiltration | Store between 2°C to 25°C (36°F to 77°F) – do not freeze; protect from light | Single-use vials of 250 IU, 500 IU, 1,000 IU, 2,000 IU, and 3,500 IU with diluent |
| coagulation factor IX – recombinant (Ixinity) | Ion exchange chromatography, solvent/detergent (SD) and nanofiltration | Store between 2°C to 25°C (36°F to 77°F) – do not freeze; protect from light. | Single-use vials contain 250 IU, 500 IU, 1,000 IU, 1,500 IU, 2,000 IU, and 3,000 IU with diluent<br>Multi-vial (2) Kit with 1,000 IU and 1,500 IU vials |
| coagulation factor IX – plasma derived (Mononine) | Immunoaffinity chromatography (IC), sodium thiocyanate and ultrafiltration | Store between 2°C to 8°C; may store at room temperature not to exceed 25°C (77°F) for up to 1 month – do not freeze | Single-dose vials contain approximately 1,000 IU with diluent |
| coagulation factor IX – plasma derived (Profilnine SD) | Solvent/detergent (SD) and nanofiltration | For 3 years or up to the expiration date as long as storage temperature does not exceed 25°C (77°F) – do not freeze | Single-dose vials of 500 IU, 1,000 IU, and 1,500 IU |
| coagulation factor IX – recombinant, Pegylated (Rebinyn) | Affinity chromatography (AC) solvent/detergent (SD) and nanofiltration | Store between 2°C to 8°C – do not freeze; may store at room temperature not to exceed 30°C (86°F) for up to 6 months; following storage at room temperature, do not refrigerate again; protect from light | Single-use vials of 500 IU, 1,000 IU, and 2,000 IU with diluent |
| coagulation factor IX – recombinant (Rixubis) | Affinity chromatography (AC), solvent/detergent (SD), and nanofiltration | Store between 2°C to 8°C – do not freeze; may store at room temperature not to exceed 30°C (86°F) for up to 36 months | Single-use vials contain 250 IU, 500 IU, 1,000 IU, 2,000 IU, and 3,000 IU with diluent |

### *Factor VIIa and Activated Prothrombin Complex Concentrate Products*

| Drug | Purification | Storage | Availability |
|---|---|---|---|
| anti-inhibitor coagulant complex – plasma derived (Feiba) | Nanofiltration and vapor heat treatment | Store at room temperature not to exceed 25°C (77°F) up to the label expiration – do not freeze; protect from light | Single-dose vials of 500 U, 1,000 U, and 2,500 U with diluent |
| coagulation factor VIIa – recombinant (NovoSeven RT) | Immunoaffinity chromatography (IC) | Store between 2°C to 25°C (36°F to 77°F) up to the label expiration date – do not freeze; protect from light | Single-dose vials of 1 mg, 2 mg, 5 mg, and 8 mg with diluent |

### *Factor IXa and Factor X Directed Antibody Products*

| Drug | Purification | Storage | Availability |
|---|---|---|---|
| emicizumab-kxwh (Hemlibra) | Not reported | Store between 2°C to 8°C – do not freeze; prior to administration may store at room temperature not to exceed 30°C (86°F) for up to 7 days; following storage at room temperature, unopened vials may be refrigerated again; protect from light | Single-dose vials of 30 mg/mL, 60 mg/0.4 mL, 105 mg/0.7 mL, and 150 mg/mL |

### *Factor X and Factor XIII Products*

| Drug | Purification | Storage | Availability |
|---|---|---|---|
| coagulation factor X - plasma derived (Coagadex) | Solvent/detergent (S/D), nanofiltration, dry heat treatment | Store between 2°C to 30°C – do not freeze; protect from light<br>Administer within 1 hour of reconstitution | Single-use vials of 250 IU and 500 IU |
| coagulation factor XIII – plasma derived (Corifact) | Ion exchange chromatography, heat-treatment, viral filtration | Store between 2°C to 8°C – do not freeze; may be stored at room temperature not to exceed 25°C (77°F) for up to 6 months, do not return to refrigeration after stored at room temperature; protect from light;<br>Administer within 4 hours after reconstitution – do not refrigerate or freeze reconstituted solution | Single-use vials of 1,000-1,600 IU |
| coagulation factor XIII A-subunit– recombinant (Tretten) | hydrophobic interaction chromatograph, ion exchange chromatography | Store between 2°C to 8°C – do not freeze; protect from light<br>Administer within 3 hours of reconstitution | Single-use vial of 2,500 IU (actual amount is 2,000 to 3,125 IU) |

***von Willebrand Products***

| Drug | Purification | Storage | Availability |
|---|---|---|---|
| von Willebrand factor – recombinant (Vonvendi) | Affinity chromatography (AC) and solvent/ detergent (SD) | Store between 2°C to 8°C – do not freeze; may store at room temperature not to exceed 30°C (86°F) for up to 12 months not past expiration date; following storage at room temperature, do not refrigerate again; protect from light | Single-dose vials in 2 vWF:RCo strengths: 650 IU (450 to 850 IU) and 1,300 IU (900 to 1,700 IU) |
| von Willebrand factor/coagulation factor VIII complex – plasma derived (Wilate) | Solvent/detergent (SD) and dry heat 2 hours at 100°C | Up to 36 months at +2°C to +8°C (36°F to 46°F) in the original containers to protect from light from the date of manufacture; may be stored for a period of up to 6 months at room temperature; once stored at room temperature, do not return to the refrigerator – do not freeze | Single-dose vial in strengths of 500 IU vWF:RCo and 500 IU factor VIII activities and 1,000 IU vWF:RCo and 1,000 IU factor VIII activities |

# CLINICAL TRIALS

## Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance. Many of the trials with agents in this class were performed in an open-label manner; introduction of bias must be considered when evaluating study findings.

The method of administration and associated monitoring makes it difficult to perform properly blinded studies with these drugs.

For the majority of factor VIII, factor IX, and factor VII products, no direct comparisons to other coagulation products have been conducted; therefore, no definitive conclusions regarding the comparative safety or efficacy can be made.

# SUMMARY

There are little direct comparative data for factor VIII, factor IX products, monoclonal antibodies, or other bypassing agents. In general, for factor VIII, there are no apparent differences in efficacy among the various products for controlling bleeding episodes with all products demonstrating a success rate

of 90% when dosed according to the patient's requirements. Factor products, with the exception of Obizur indicated only for the extremely rare acquired hemophilia A, may be considered interchangeable in efficacy, although other issues are also important when considering product selection. These may include purification processes and the perception of purity, as well as potential inhibitor development. Additional considerations include, but are not limited to, patient and/or physician preference, vial size for dosing convenience, cost, and product availability. The impact of the new FC fusion protein, albumin fusion protein, single-chain formulation, and PEGylated products designed to increase factor half-life has yet to be defined. In general, evidence to date for the extended half-life products is inconclusive. While half-lives have shown increases for several of the factor IX products, increases for factor VIII have been incremental at best. Similarly, the impact of the monoclonal antibody Hemlibra (emicizumab-kxwh) has yet to be determined. It is approved for use in adults and children of all ages as routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia A patients with or without inhibitors, and provides dosing regimens of once every 1, 2, or 4 weeks. Patient specifics, including product impact on annualized spontaneous bleed rates, remain important indicators of product efficacy of all hemophilia treatment products.

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