



Hemophilia and Related Agents Therapeutic Class Review (TCR)

September 8, 2022

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FDA-APPROVED INDICATIONS

Factor VIII Products

Drug	Manufacturer	Indications
antihemophilic factor VIII - recombinant (Advate®) ¹	Baxalta	<ul style="list-style-type: none"> Control and prevention of bleeding episodes in adults and children with hemophilia A (classical hemophilia) Perioperative management in adults and children with hemophilia A Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A Not indicated for von Willebrand disease (vWD)
antihemophilic factor VIII – recombinant, PEGylated (Adynovate®) ²	Baxalta	<ul style="list-style-type: none"> Control and prevention of bleeding episodes in adults and adolescents ≥ 12 years of age with hemophilia A Perioperative management in adults and children with hemophilia A Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A Not indicated for vWD
antihemophilic factor VIII – recombinant, single chain (Afstyla®) ³	CSL Behring	<ul style="list-style-type: none"> Prevention and control of bleeding episodes in adults and children with hemophilia A Perioperative management in adults and children with hemophilia A Routine prophylaxis therapy to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A Not indicated for vWD
antihemophilic factor VIII/ von Willebrand factor complex – plasma derived (Alphanate®) ⁴	Grifols	<ul style="list-style-type: none"> Control and prevention of bleeding episodes in hemophilia A 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	<ul style="list-style-type: none"> Prevention and control of bleeding episodes in adults and children with hemophilia A Perioperative management in adults and children with hemophilia A Routine prophylaxis therapy to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A Not indicated for vWD
antihemophilic factor – recombinant, glycopegylated-exei (coagulation factor VIII concentrate) (Esperoct®) ⁶	Novo Nordisk	<ul style="list-style-type: none"> On-demand treatment and control of bleeding episodes in adults and children with hemophilia A Perioperative management of bleeding in adults and children with hemophilia A Routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia A Not indicated for the treatment of vWD
antihemophilic factor VIII – plasma derived (Hemofil M®) ⁷	Baxalta	<ul style="list-style-type: none"> Control and prevention of hemorrhagic episodes in hemophilia A Not indicated for vWD

Factor VIII Products (continued)

Drug	Manufacturer	Indications
antihemophilic factor VIII – plasma derived (Humate-P®) ⁸	CSL Behring	<ul style="list-style-type: none"> • Treatment and prevention of bleeding in adults with hemophilia A • 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 • Not indicated for the prophylaxis of spontaneous bleeding episodes in vWD
antihemophilic factor VIII – recombinant, PEGylated (Jivi®) ⁹	Bayer Healthcare	<ul style="list-style-type: none"> • Control and prevention of bleeding episodes in adults and adolescents ≥ 12 years of age with hemophilia A • Perioperative management in adults and adolescents ≥ 12 years of age with hemophilia A • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and adolescents ≥ 12 years of age with hemophilia A • Not indicated for use in previously untreated patients • Not indicated for vWD
antihemophilic factor VIII – plasma derived (Koate®) ¹⁰	Kedrion Biopharma	<ul style="list-style-type: none"> • Control and prevention of bleeding episodes or in order to perform emergency and elective surgery on individuals with hemophilia A • Not approved for use in vWD
antihemophilic factor VIII – recombinant (Kogenate FS®) ¹¹	Bayer Healthcare	<ul style="list-style-type: none"> • Control and prevention of bleeding episodes in adults and children with hemophilia A • Perioperative management in adults and children with hemophilia A • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in children with hemophilia A and reduce the risk of joint damage in children showing no preexisting joint damage • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults with hemophilia A • Not indicated for vWD
antihemophilic factor VIII – recombinant (Kovaltry®) ¹²	Bayer Healthcare	<ul style="list-style-type: none"> • Control and prevention of bleeding episodes in adults and children with hemophilia A • Perioperative management of bleeds in adults and children with hemophilia A • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults with hemophilia A • Not indicated for vWD
antihemophilic factor VIII – recombinant (Novoeight®) ¹³	Novo Nordisk	<ul style="list-style-type: none"> • On-demand treatment and control of bleeding episodes in adults and children with hemophilia A • Perioperative management in adults and children with hemophilia A • Routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia A • Not indicated for vWD

Factor VIII Products (continued)

Drug	Manufacturer	Indications
antihemophilic factor VIII – recombinant (Nuwiq®) ¹⁴	Octapharma	<ul style="list-style-type: none"> Control and prevention of bleeding episodes in adults and children with hemophilia A Perioperative bleed management in adults and children with hemophilia A Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A Not indicated for vWD
antihemophilic factor VIII – recombinant, porcine sequence (Obizur®) ¹⁵	Baxalta	<ul style="list-style-type: none"> For the on-demand treatment and control of bleeding episodes in adults with acquired hemophilia A Safety and efficacy have not been established in patients with a baseline anti-porcine factor VIII inhibitor titer of greater than 20 BU Not indicated for the treatment of congenital hemophilia A or vWD
antihemophilic factor VIII – recombinant (Recombinate®) ¹⁶	Baxalta	<ul style="list-style-type: none"> Control and prevention of hemorrhagic episodes in hemophilia A in adults and children Perioperative management in patients with hemophilia A Not indicated for vWD
antihemophilic factor VIII – recombinant (Xyntha®) ^{17,18}	Wyeth/Pfizer	<ul style="list-style-type: none"> Control and prevention of bleeding episodes in adults and children with hemophilia A Perioperative management in adults and children with hemophilia A For routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia A Not indicated for vWD

Factor IX Products

Drug	Manufacturer	Indications
coagulation factor IX – plasma derived (AlphaNine SD®) ¹⁹	Grifols	<ul style="list-style-type: none"> Prevention and control of bleeding in patients ≥ 17 years of age with factor IX deficiency due to hemophilia B 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 Not indicated for the reversal of coumarin anticoagulant-induced hemorrhage, nor for the treatment of hemophilia A patients with inhibitors to factor VIII
coagulation factor IX – recombinant, FC fusion protein (Alprolix®) ²⁰	Bioverativ	<ul style="list-style-type: none"> Prevention and control of bleeding episodes in adults and children with factor IX deficiency, hemophilia B Perioperative management in adults and children with hemophilia B Routine prophylaxis therapy to prevent or reduce the frequency of bleeding episodes in adults and children with factor IX deficiency, hemophilia B Not indicated for induction of immune tolerance therapy in patients with hemophilia B
coagulation factor IX – recombinant (BeneFIX®) ²¹	Wyeth/Pfizer	<ul style="list-style-type: none"> On-demand treatment and control of bleeding episodes in adults and pediatric patients with hemophilia B Perioperative management of bleeding in adults and pediatric patients with hemophilia B Routine prophylaxis to reduce the frequency of bleeding episodes in patients 16 years of age and older with hemophilia B Not indicated for induction of immune tolerance in patients with hemophilia B

Factor IX Products (continued)

Drug	Manufacturer	Indications
coagulation factor IX – recombinant, albumin fusion protein (Idelvion®) ²²	CSL Behring	<ul style="list-style-type: none"> Prevention and control of bleeding episodes in adults and children with hemophilia B Perioperative management in adults and children with hemophilia B Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia B Not indicated for induction of immune tolerance therapy in patients with hemophilia B
coagulation factor IX – recombinant (Ixinity®) ²³	Aptevo BioTherapeutics and Medexus	<ul style="list-style-type: none"> On-demand treatment and control of bleeding episodes in adults and pediatric patients ≥ 12 years of age with hemophilia B Perioperative management in adults and pediatric patients ≥ 12 years of age with hemophilia B Routine prophylaxis to reduce the frequency of bleeding episodes in adults and pediatric patients ≥ 12 years of age with hemophilia B Not indicated for the induction of immune tolerance therapy in patients with hemophilia B
coagulation factor IX – plasma derived (Profilnine®) ²⁴	Grifols	<ul style="list-style-type: none"> Prevention and control of bleeding in patients with factor IX deficiency due to hemophilia B Not indicated for use in the treatment of factor VII deficiency
coagulation factor IX – recombinant, PEGylated (Rebinyn®) ²⁵	Novo Nordisk	<ul style="list-style-type: none"> On-demand treatment and control of bleeding episodes in adults and children with factor IX deficiency, hemophilia B Perioperative management in adults and children with factor IX deficiency, hemophilia B Routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with congenital factor IX deficiency, hemophilia B Not indicated for induction of immune tolerance therapy in patients with hemophilia B
coagulation factor IX – recombinant (Rixubis®) ²⁶	Baxalta	<ul style="list-style-type: none"> Prevention and control of bleeding episodes in adults and children with factor IX deficiency, hemophilia B Perioperative management in adults and children with hemophilia B Routine prophylaxis therapy to prevent or reduce the frequency of bleeding episodes in adults and children with factor IX deficiency, hemophilia B 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 2018.²⁷ CSL Behring discontinued distribution of Monoclate P®; supply was estimated to be depleted by December 2018.²⁸ CSL Behring discontinued Hexilate FS in 2018; supply was anticipated to be exhausted in early 2019.²⁹ CSL Behring announced in 2020 that Mononine would be discontinued; product remained available until at least mid-2021.³⁰

Factor VIIa and Activated Prothrombin Complex Concentrate Products

Drug	Manufacturer	Indications
activated prothrombin complex - plasma derived (Feiba®) ³¹	Baxalta	<ul style="list-style-type: none"> Control and prevention of bleeding episodes in hemophilia A and hemophilia B patients with inhibitors Perioperative management in hemophilia A and hemophilia B patients with inhibitors Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia A and hemophilia B patients with inhibitors 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®) ³²	Novo Nordisk	<ul style="list-style-type: none"> Treatment of bleeding episodes in hemophilia A or B with inhibitors and in acquired hemophilia Prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B with inhibitors and in acquired hemophilia Treatment of bleeding episodes in congenital factor VII deficiency Prevention of bleeding in surgical interventions or invasive procedures in congenital FVII deficiency Treatment of Glanzmann's Thrombasthenia with refractoriness to platelet transfusions with or without antibodies
coagulation factor VIIa – recombinant-jncw (Sevenfact®) ³³	Hema	<ul style="list-style-type: none"> Treatment and control of bleeding episodes occurring in adults and adolescents (≥ 12 years of age) with hemophilia A or B with inhibitors Not indicated for treatment of congenital factor VII deficiency

Factor IXa and Factor X Directed Antibody Products

Drug	Manufacturer	Indications
emicizumab-kxwh (Hemlibra®) ³⁴	Genentech	<ul style="list-style-type: none"> 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®) ³⁵	Bio Products Laboratory	<ul style="list-style-type: none"> Routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with heredity factor X deficiency On-demand treatment and control of bleeding episodes in adults and children with heredity factor X deficiency Perioperative management of bleeding in patients with mild and moderate hereditary factor X deficiency in adults and children with heredity factor X deficiency 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®) ³⁶	CSL Behring	<ul style="list-style-type: none"> Routine prophylactic treatment for adult and pediatric patients with congenital factor XIII deficiency Perioperative management of surgical bleeding in adult and pediatric patients with congenital XIII deficiency
coagulation factor XIII A-subunit– recombinant (Tretten®) ³⁷	Novo Nordisk	<ul style="list-style-type: none"> Routine prophylaxis of bleeding in patients with congenital factor XIII A-subunit deficiency Not indicated for use in patients with congenital factor XIII B-subunit deficiency

Von Willebrand Products

Drug	Manufacturer	Indications
von Willebrand factor - recombinant (Vonvendi®) ³⁸	Baxalta	<ul style="list-style-type: none"> For on-demand treatment and control of bleeding episodes in adults (age 18 and older) with vWD Perioperative management of bleeding in adults (age ≥ 18) with vWD Routine prophylaxis to reduce the frequency of bleeding episodes in patients with severe type 3 vWD receiving on-demand therapy
von Willebrand factor/coagulation factor VIII complex –plasma derived (Wilate®) ³⁹	Octapharma	<ul style="list-style-type: none"> For on-demand treatment and control of bleeding episodes in children and adults with vWD Perioperative management of bleeding in children and adults with vWD Routine prophylaxis to reduce the frequency of bleeding episodes in adolescents and adults with hemophilia A For on-demand treatment and control of bleeding episodes in adolescents and adults with hemophilia A

OVERVIEW^{40,41,42,43,44,45,46,47,48,49,50,51,52}

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 male 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 up to 33,000 males 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 (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 (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 (< 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 (WFH) 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; and 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 (#272) with recommendations regarding products used for the treatment of hemophilia and other bleeding disorders in April 2022. 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 animal 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 state 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 seems to have substantially decreased the risk for 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 states 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) were published in the *New England Journal of Medicine*. The SIPPET trial was a prospective randomized study that collected data from a large multi-national group of previously-untreated patients with hemophilia A between January 2010 and December 2014. 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, 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 compared with 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 (US) 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 and 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 April 2022, 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 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 with Hemlibra; 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, superior efficacy). Infants should be considered for prophylaxis with Hemlibra therapy 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.

The 2022 MASAC guidelines provide recommendations regarding prophylaxis for patients with hemophilia A or B with and without inhibitors. 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 can also be used in patients with mild or moderate hemophilia who have a severe phenotype. Prophylactic therapy should be initiated early (e.g., prior to the age of 3 years and before the second joint bleed) and may be considered within the first 6 months after birth to decrease the potential for intracranial hemorrhage (e.g., emicizumab prophylaxis for hemophilia A). Prophylactic options include standard half-life factor, extended half-life factor, and non-factor replacement (emicizumab). Bypassing agents (BPAs) may be used for prophylaxis in those with inhibitors; however, for hemophilia A patients with inhibitors, BPAs

are less effective than prophylaxis with emicizumab. For prophylaxis in hemophilia A patients, standard half-life factors are usually given 2 to 4 times per week, and extended half-life factors are usually given 1 to 3-times per week with the goal trough values for factor VIII levels of at least 1% (> 3% to 5% or higher if possible) and minimal or no spontaneous bleeds. When factors are utilized for prophylaxis, the dose and frequency can be individualized based on pharmacokinetic studies. In contrast, laboratory-based assays are not currently approved for assessing response in patients receiving non-factor replacement (emicizumab). Standard half-life and extended half-life factor VIII prophylaxis can be given in the morning to prevent bleeding events during the day; however, timing of the dose is not considered as relevant for the extended half-life factor IX products. Adherence to prophylactic regimens should be monitored, and a patient's regimen may need to be adjusted across the patient's life based on changes in physical activity and risk of traumatic bleeding. The WFH guidelines describe factors for individualization of prophylaxis: patient's bleeding phenotype, joint status, pharmacokinetics, and preference. If a patient continues to experience bleeding, the prophylactic regimen should be increased, including the dose/frequency or both. There are no definitive guidelines for stopping prophylactic dosing and some individuals may require this modality for their entire life. Where applicable, prophylaxis dosing recommendations from manufacturers for specific factor products is summarized in the table below.

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 hemostatic 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 deficiency of qualitatively normal vWF 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. Main approaches for the treatment of vWD include increasing plasma concentrations of vWF through stimulation with desmopressin (DDAVP); replacing vWF by using human plasma-derived viral inactivated concentrates or recombinant vWF concentrate; and promoting hemostasis by utilizing hemostatic agents with mechanisms other than increasing vWF. Regular prophylaxis for von Willebrand patients is seldom required. The American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the WFH published guidelines on the management of vWD in 2021 with detailed recommendations for various patient populations including surgery, pregnancy, and post-partum.⁵³

PHARMACOLOGY^{54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89}

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. 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, it is considered a first generation product. 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. 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 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 is a human plasma-derived product 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 is also a human plasma-derived product 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 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.

There are also 3 agents considered to be bypassing agents; these agents do not replace a missing factor, but instead bypass the need for factor VIII or IX, when the factors are being blocked by an inhibitor. Thereby, the bypassing agents allow clotting to occur. There are currently 2 recombinant coagulation factor VIIa products available: NovoSeven RT and Sevenfact. The plasma-derived, activated prothrombin complex concentrate, Feiba, is also considered a bypassing agent.

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 make 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 defer 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 considered 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 of 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^{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; emicizumab-kxwh has not been evaluated in patients with severe hepatic or renal impairment. However, the predicted concentration in patients younger than 6 months was reported to be 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}

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 signs 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. Labeling for Sevenfact advises that patients with known immunoglobulin E (IgE)-based hypersensitivity to casein may be at higher risk of hypersensitivity reactions. Sevenfact is also contraindicated in patients with known allergy to rabbits or rabbit proteins.

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 and 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. Labeling for the factor VIII product, Eloctate, has been updated to include warnings in regard to cardiovascular risk factors (hemophilic patients with these risk factors carry the same risk for developing cardiovascular events as non-hemophilic patients once normalization of clotting occurs through receipt of factor VIII) and catheter-related complication (consider potential for central venous access device [CVAD]-related complications if one is required).

Emicizumab-kxwh (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.¹⁶⁰ Thrombotic events were also reported in the course of clinical trials of Hemlibra when patients again received aPCC in an average cumulative amount greater than 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. As emicizumab-kxwh has a long half-life, the potential for an interaction with aPCC (e.g., TMA or thromboembolism) may continue for up to 6 months following the final dose.

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 RT 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.

Sevenfact also carries a boxed warning for thrombosis. Arterial or venous thrombotic events were not reported in Sevenfact clinical trials, which excluded patients with a history of these events. Labeling warns of increased risk in patients with a history of: (1) congenital or acquired hemophilia who are also treated with hemostatic agents, such as activated or non-activated prothrombin complex (aPCC/PCC); or (2) atherosclerotic disease, coronary artery disease, cerebrovascular disease, crush injury, septicemia, or thromboembolism. Patients should be carefully monitored for any signs or symptoms indicating activation of the coagulation system or development of thrombosis.

DRUG INTERACTIONS^{161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195}

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.

Factor VIIa products used in combination with activated prothrombin complex concentrate increases the risk for serious thrombotic events; therefore, simultaneous use should be avoided.

ADVERSE EFFECTS^{196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246}

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, which 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 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 a failure to adequately respond to normal factor concentrate replacement dose in a patient who previously demonstrated a positive clinical response, 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', 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 \geq 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, and the anti-Hemlibra antibody positivity rate could potentially be under-reported due to limitations of the assay utilized. In April 2018 MASAC issued updated safety information for Hemlibra addressing the detection of anti-drug antibodies.²⁴⁷ 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. An 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. In December 2021, Hemlibra labeling was updated to state that antidrug antibodies occurred in 5.1% of patients (34/668) in phase 3 clinical studies, and although most patients with these antibodies did not exhibit a change in plasma levels of emicizumab or an increase in bleeding events, in <1% of cases, the neutralizing antibodies resulted in decreased drug levels and could be associated with loss of efficacy. As a result, monitor for an increase

in breakthrough bleeding events due to loss of efficacy and evaluate the underlying cause if breakthrough bleeding events occur. If neutralizing antidrug antibodies are suspected, a change in therapy may be warranted.

SPECIAL POPULATIONS^{248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282}

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, Profilnine, 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, Sevenfact, 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^{283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327}

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 WFH guidelines state the standard of care for all patients with severe hemophilia is prophylaxis with clotting factor concentrates (CFCs) or other hemostatic products to prevent bleeding; therapy should be initiated before 3 years of age to prevent musculoskeletal complications caused by recurrent joint or muscle bleeds. Furthermore, episodic or “on demand” clotting factor replacement therapy is no longer considered a long-term treatment option.

General dosing information for hemophilia A or B 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.

Manufacturer Recommended Prophylaxis Dosing

Factor VIII Products

Drug	Manufacturer Recommended Starting Doses for Prophylaxis
antihemophilic factor VIII – recombinant (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% Adjust dosing based on patient’s clinical response
antihemophilic factor VIII – recombinant, PEGylated (Adynovate)	For adults and adolescents (≥ 12 years): 40 to 50 IU/kg 2 times a week For children < 12 years: start with 55 IU/kg 2 times a week with maximum of 70 IU/kg Adjust dosing and dosing intervals based on patient’s clinical response
antihemophilic factor VIII – recombinant, single chain (Afstyla)	For children < 12 years: 30 to 50 IU/kg 2 to 3 times a week For adults and adolescents ≥ 12 years: 20 to 50 IU/kg 2 to 3 times a week Adjust dosing based on patient’s clinical response
antihemophilic factor VIII/ von Willebrand factor complex – plasma derived (Alphanate)	Dose (units) = body weight (kg) x desired FVIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) 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 (Eloctate)	For children and adults: 50 IU/kg every 4 days Adjust dosing based upon patient’s clinical response Dosing range based upon response may be adjusted within 25 to 65 IU/kg every 3 to 5 days Doses of up to 80 IU/kg with greater frequency may be required for children < 6 years of age
antihemophilic factor – recombinant, glycopegylated-exei (Esperoct)	For children < 12 years: 65 IU/kg twice weekly For adults and adolescents ≥ 12 years: 50 IU/kg every 4 days 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 (Hemofil M)	N/A
antihemophilic factor VIII – plasma derived (Humate-P)	N/A
antihemophilic factor VIII – recombinant, PEGylated (Jivi)	For adults and adolescents ≥ 12 years: 30 to 40 IU/kg 2 times a week Based on bleeding episodes, regimen may be adjusted to 45 to 60 IU/kg every 5 days Adjust dosing and frequency based on patient’s clinical response
antihemophilic factor VIII – plasma derived (Koate DVI)	N/A
antihemophilic factor VIII – recombinant (Kogenate FS)	For children: 25 IU/kg every other day 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 For adults and adolescents ≥ 12 years: 20 to 40 IU/kg 2 to 3 times a week Adjust dosing based on patient’s clinical response

Factor VIII Products (continued)

Drug	Manufacturer Recommended Starting Doses for Prophylaxis
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 For adults and children ≥ 12 years: 20 to 40 IU/kg every other day or 20 to 50 IU/kg 3 times a week 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 For adults and children ≥ 12 years: 30 to 40 IU/kg every other day 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 For children < 12 years: 25 IU/kg every other day More frequent or higher doses may be needed in children < 12 years due to the higher clearance in this patient population 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 Adjust dosing based upon patient’s clinical response
coagulation factor IX – recombinant (BeneFIX)	For children and adults: 100 IU/kg once weekly Patients < 12 years have lower recovery, shorter half-life, and higher clearance (based on per kg body weight) as compared to adolescents and adults The dosing regimen (dose or frequency) should be adjusted based on the patient’s clinical response
coagulation factor IX – recombinant, albumin fusion protein (Idelvion)	For children < 12 years of age: 40 to 55 IU/kg every 7 days 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 Adjust dosing based on patient’s clinical response
coagulation factor IX – recombinant (Ixinity)	For previously treated patients: 40 to 70 IU/kg twice weekly; adjust dosing based on the patient’s age, bleeding pattern, and physical activity
coagulation factor IX – plasma derived (Profilnine)	N/A

Factor IX Products (continued)

Drug	Manufacturer Recommended Starting Doses for Prophylaxis
coagulation factor IX – recombinant, Pegylated (Rebinyn)	For children and adults: 40 IU/kg body weight once weekly; adjust dosing based on patient’s bleeding pattern and physical activity
coagulation factor IX – recombinant (Rixubis)	For patients < 12 years of age previously treated with factor IX: 60 to 80 IU/kg twice a week For patients ≥ 12 years previously treated with factor IX: 40 to 60 IU/kg twice a week 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; Adjust dosing based on patient’s clinical response 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
coagulation factor VIIa – recombinant-jncw (Sevenfact)	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 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 (Coagadex)	Age ≥ 12 years: 25 IU/kg twice weekly Age < 12 years: 40 IU/kg twice weekly 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 (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 Administer every 28 days for routine prophylaxis 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 (Tretten)	35 IU/kg once monthly to achieve a target trough level of FXIII activity ≥ 10% using a validated assay; 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 (Vonvendi)	For adults: initiate with 40 to 60 IU/kg twice weekly; adjust dose up to 60 IU/kg twice weekly if breakthrough bleeding occurs in joints or if severe bleeding occurs; breakthrough bleeding should be treated as described in the product labeling
von Willebrand factor/coagulation factor VIII complex – plasma derived (Wilate)*	For adults and adolescents ≥ 12 years: 20 to 40 IU/kg every 2 to 3 days 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 prothrombin complex concentrates (PCC) products, commonly referred to as bypassing agents have unique dosing recommendations for the treatment of bleeding episodes in hemophilia A and 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:

$$\text{Weight in pounds} \div 4.4 \times \text{factor level desired} = \text{factor VIII units required}$$

or

$$\text{body weight (kg)} \times \text{desired factor VIII increase (IU/dL or \% normal)} \times 0.5 \text{ (IU/kg per IU/dL)}$$

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:

$$\text{Estimated increment of factor X (IU/dL or \% of normal)} = [\text{Total dose (IU)}/\text{body weight (kg)}] \times 2$$

For patients < 12 years of age:

$$\text{Estimated increment of factor X (IU/dL or \% of normal)} = [\text{Total dose (IU)}/\text{body weight (kg)}] \times 1.7$$

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:

$$\text{Dose (IU)} = \text{body weight (kg)} \times \text{desired factor X rise (IU/dL or \% of normal)} \times 0.5$$

For patients < 12 years of age:

$$\text{Dose (IU)} = \text{Body weight (kg)} \times \text{desired factor X rise (IU/dL)} \times 0.6$$

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:

$$\text{Weight in pounds} \div 2.2 \times \text{factor level desired} = \text{factor IX units required}$$

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.³²⁸ 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 induced a response, the development of an inhibitor must be suspected as these may be considered the most severe treatment-related complication in hemophilia.

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, Sevenfact) 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 are similar, but rate of success has proven to be 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 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/ von Willebrand factor complex – 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
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

Factor VIII Products (continued)

Drug	Purification	Storage	Availability
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)	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 a needleless reconstitution system in strengths of 250 IU, 500 IU, 1,000 IU, 2,000 IU, and 3,000 IU
antihemophilic factor VIII – recombinant (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

Factor VIII Products (continued)

Drug	Purification	Storage	Availability
antihemophilic factor VIII Recombinant (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, 1,500 IU , 2,000 IU, 2,500 IU, 3,000 IU, and 4,000 IU
antihemophilic factor VIII – recombinant, porcine sequence (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 (Recombinate)	Immunoaffinity chromatography (IC) 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 (Xyntha)	Affinity chromatography (AC) solvent/detergent (SD) and nanofiltration	Up to 36 months at +2°C to +8°C (36°F to 46°F) until expiration date 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 Multi-vial (2) Kit with 1,000 IU and 1,500 IU vials
coagulation factor IX – plasma derived (Profilnine)	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, 2,000 IU, and 3,000 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

*FDA approved but not yet commercially available as of September 2022.

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
coagulation factor VIIa – recombinant-jncw (Sevenfact)	Enzymatic	Store between 2°C to 30°C (36°F to 86°F) – do not freeze; protect from light; after reconstitution, store at room temperature or can be stored 2°C to 30°C for up to 4 hours	Single-dose vials of 1 mg and 5 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 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; 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 chromatography, ion exchange chromatography	Store between 2°C to 8°C – do not freeze; protect from light 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 products, 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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Etranacogene dezaparvovec-drlb (Hemgenix®) New Drug Update

January 2023

Nonproprietary Name	etranacogene dezaparvovec-drlb
Brand Name	Hemgenix
Manufacturer	CSL Behring
Form	Suspension for intravenous (IV) infusion; single-use vial
Strength	1 x 10 ¹³ genome copies (gc)/mL
FDA Approval	November 22, 2022
Market Availability	Available
FDA Approval Classification	Breakthrough Therapy, Orphan Drug, Priority Review
FDB Classification- Specific Therapeutic Class (HIC3)	Gene Therapy Agents – Factor IX Deficiency (M0V)

INDICATION¹

Etranacogene dezaparvovec-drlb (Hemgenix) is an adeno-associated virus (AAV) vector-based gene therapy indicated for treatment of adults with hemophilia B (congenital factor IX deficiency) who currently use factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage or repeated, serious spontaneous bleeding episodes.

PHARMACOKINETICS

In the clinical trial, factor IX protein expression was detectable by week 3 and factor IX activity levels reached a mean of 39% of normal at 6 months. A total of 56% of subjects achieved absence of vector DNA from blood and 69% from semen by month 24.

CONTRAINDICATIONS/WARNINGS

There are no known contraindications to etranacogene dezaparvovec-drlb.

Infusion reactions, including hypersensitivity reactions and anaphylaxis, may occur. Patients should be monitored during administration and for at least 3 hours after end of infusion. The product should not be infused faster than 500 mL/hour. If symptoms occur, administration should be slowed or interrupted. If interrupted, administration at a slower infusion can be restarted once infusion reactions resolve. Treatment with a corticosteroid or antihistamine for management of an infusion reaction should be considered.

Transaminase levels should be closely monitored once per week for 3 months after administration to mitigate the risk of potential hepatotoxicity. In clinical studies, most subjects had asymptomatic and predominately mild elevations in transaminases. Most often, elevated ALT levels occurred in the first 4

months after administration. Providers should continue to monitor transaminases in all patients who developed liver enzyme elevations until liver enzymes return to baseline levels and consider corticosteroid treatment should elevations occur.

In AAV-vector based gene therapies, preexisting neutralizing anti-AAV antibodies may obstruct transgene expression at therapeutic levels. Following treatment, all patients developed neutralizing anti-AAV antibodies. Re-administration of etranacogene dezaparvovec-drlb in the presence of high anti-AAV5 antibody titer has not been evaluated. A validated neutralizing anti-AAV5 antibody assay is not currently available. Patients who intend to receive etranacogene dezaparvovec-drlb are encouraged to enroll in a study that evaluates the effect of pre-existing anti-AAV5 neutralizing antibodies on the risk of bleeding.

Etranacogene dezaparvovec-drlb carries the theoretical risk of hepatocellular carcinoma development. For patients with preexisting risk factors (e.g., cirrhosis, advanced hepatic fibrosis, hepatitis B or C, non-alcoholic fatty liver disease [NAFLD], chronic alcohol consumption, non-alcoholic steatohepatitis [NASH], and advanced age), perform regular (e.g., annual) liver ultrasound and alpha-fetoprotein (AFP) testing in the 5 years following administration.

DRUG INTERACTIONS

There are no known drug interactions associated with etranacogene dezaparvovec-drlb.

COMMON ADVERSE EFFECTS

The most common adverse reactions (incidence \geq 5%) reported in clinical studies were ALT elevation (42%), AST elevation (42%), blood creatine kinase elevation (42%), infusion-related reactions (33%), headache (18%), flu-like symptoms (14%), fatigue (12%), malaise (12%), and nausea (7%).

SPECIAL POPULATIONS

Pregnancy

Etranacogene dezaparvovec-drlb is not intended for use in women; data in pregnancy are inadequate to advise of maternal or fetal risk.

Pediatrics

Safety and efficacy of etranacogene dezaparvovec-drlb have not been established in pediatric patients (\leq 18 years of age).

Geriatrics

In clinical trials, no difference in pharmacokinetic profiles of etranacogene dezaparvovec-drlb were reported between patients \geq 65 years of age and younger populations.

Hepatic Impairment

Safety and efficacy in patients with advanced hepatic impairment, including uncontrolled hepatitis B and C, have not been investigated.

Renal Impairment

Safety and efficacy in patients with severe renal impairment and end-stage renal disease have not been investigated. Subjects with mild and moderate renal impairment were included in clinical trials.

DOSAGES

Etranacogene dezaparvovec-drlb is given once as a single dose by intravenous (IV) infusion. The recommended dose is 2×10^{13} genome copies (gc) per kilogram (kg) of body weight (or 2 mL/kg body weight).

Prior to the start of therapy, patients should be screened for factor IX inhibitors. Do not administer if both the initial and re-test results are positive. After administration, providers should regularly monitor (e.g., weekly for 3 months) factor IX activity as it may take several weeks before improved hemostatic control is observed. Continued support with exogenous human factor IX may be needed during the first weeks of infusion. It is recommended to use the same assay and reagents to monitor factor IX activity over time.

Providers should also monitor for the development of inhibitors to factor IX after administration through clinical observations and laboratory tests.

CLINICAL TRIALS^{2,3,4}

A literature search was performed using “etranacogene dezaparvovec-drlb” and “hemophilia.”

HOPE-B (NCT03569891) is an ongoing, phase 3, open-label, single-dose, single-arm, multinational clinical trial to evaluate the safety and efficacy of etranacogene dezaparvovec-drlb. Fifty-four adult male patients with hemophilia B classified as having moderately severe or severe hemophilia B and requiring prophylactic factor IX replacement therapy were enrolled. Patients prospectively completed a lead-in period of at least 6 months during which time they continued to use their current standard of care therapy to establish a baseline annualized bleeding rate (ABR). After completing the lead-in period, participants received a single IV dose of etranacogene dezaparvovec-drlb (2×10^{13} gc/kg dose), and were followed monthly until month 12, then at 6-month intervals until year 5.

Eighteen months of post-treatment data were used for the efficacy evaluation. The primary endpoint was a non-inferiority test of ABR during months 7 to 18 after treatment compared with ABR during the 6-month lead-in period. Secondary endpoints included assessment of factor IX activity.

Patients were allowed to continue prophylaxis during months 0 to 6. Two patients were not able to stop routine prophylaxis after treatment. During months 7 to 18, an additional patient received prophylaxis from days 396 to 534 (approximately 20 weeks). Patients with and without pre-existing neutralizing antibodies to AAV5 were evaluated.

Results from the HOPE-B trial demonstrated non-inferiority of etranacogene dezaparvovec-drlb after 7 to 18 months compared to the lead-in period. Seven to 18 months post infusion, the mean adjusted ABR was 1.9 bleeds per year after etranacogene dezaparvovec-drlb treatment, compared with an ABR of 4.1 bleeds per year during the lead-in period; a reduction of 54%. After 24 months of follow-up, the observed reduction in ABR was 64%. Among study participants, 74% had bleeds in the lead-in period and 37% had bleeds 7 to 18 months after treatment. In addition, 96.3% (52 out of 54) of patients discontinued use of factor IX prophylaxis and remained free of previous continuous routine prophylaxis therapy.

OTHER DRUGS USED FOR CONDITION^{5,6}

Currently, patients with hemophilia B receive IV infusions of factor IX prophylaxis therapy. Standard half-life recombinant (e.g., Benefix[®], Ixinity[®], Rixubis[®]), extended half-life (e.g., Alprolix[®], Idelvion[®], Rebinyn[®]), and plasma-derived factor IX products (e.g., AlphaNine[®], Mononine[®]) are available. Patients with inhibitors are treated with bypassing agents (e.g., Feiba[®], NovoSeven[®], SevenFact[®]).

PLACE IN THERAPY^{7,8,9,10,11}

Hemophilia B (factor IX deficiency) is an X-linked inherited coagulation factor deficiency that results in a lifelong bleeding disorder. Hemophilia affects more than 1.2 million individuals (mostly males) worldwide and hemophilia B occurs in approximately 1 in 15,000 to 1 in 30,000 live male births. All races and ethnic groups are affected. Severe disease (factor IX activity <1% of normal) occurs in approximately 30% to 50% of patients. As an X-linked, recessive disorder, females are typically asymptomatic carriers but may have mild disease. The hallmark of hemophilia is spontaneous bleeding or bleeding disproportionate to trauma. Joint and muscle hemorrhage occur more commonly in moderate and severe hemophilia.

The National Hemophilia Foundation (NHF) Medical and Scientific Advisory Council (MASAC) recommends bleeding prophylaxis be initiated at a young age (e.g., ≤ age 3 years and prior to second joint bleed) in individuals with severe hemophilia or with mild or moderate hemophilia with a severe phenotype. Standard of care includes plasma-derived or recombinant factor IX replacement infused as often as twice a week. Dosing and frequency are adjusted to target therapy goals including trough factor levels of at least 1% (>3% to 5%, or higher if feasible) and minimal to no spontaneous bleeding. Hypersensitivity reactions, antibody formation, and thrombosis are concerns with factor products.

Etranacogene dezaparvovec-drlb (Hemgenix) is the first FDA-approved gene therapy for the treatment of hemophilia B. Etranacogene dezaparvovec-drlb has been shown to reduce the rate of annual bleeds and substantially reduce the need for prophylactic therapies. The approval of IV etranacogene dezaparvovec-drlb provides a one-time treatment alternative to the burdensome routine factor IX infusions currently used for the treatment of hemophilia B. The benefits of etranacogene dezaparvovec-drlb have been sustained for 2 years in the ongoing HOPE-B trial. Longer-term data beyond 24 months is currently lacking to demonstrate durability of response. The estimated study completion date of HOPE-B is March 2025.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Hemophilia Agents
Clinical Edit	<p>Initial Approval Criteria</p> <ul style="list-style-type: none"> ▪ Patient is at least 18 years of age; AND ▪ Prescribed by a hematologist and patient is managed by a hemophilia treatment center; AND ▪ Patient has a diagnosis of moderately severe or severe congenital factor IX deficiency (e.g., factor IX $\leq 2\%$), as confirmed by blood coagulation testing (<i>Note: Not intended for use in women</i>); AND ▪ Patient has one or more of the following: <ul style="list-style-type: none"> ○ Currently uses factor IX prophylaxis therapy; OR ○ Current or historical life-threatening hemorrhage; OR ○ Repeated, serious spontaneous bleeding episodes; AND ▪ Patient has been tested and found negative for factor IX inhibitor titers (if test result is positive, re-test within approximately 2 weeks. If re-test is also positive, Hemgenix should not be given); AND ▪ Patient factor IX (FIX) activity will be monitored periodically (e.g., weekly for 3 months); AND ▪ Provider will monitor for presence of inhibitors if bleeding is not controlled (<i>Note: Patients will continue to require exogenous factor IX until response to Hemgenix occurs</i>); AND ▪ Patient will have baseline liver function assessed prior to and after therapy, weekly, for ≥ 3 months; AND ▪ Patients with preexisting risk factors for hepatocellular carcinoma (e.g., cirrhosis, advanced hepatic fibrosis, hepatitis C or B, non-alcoholic fatty liver disease [NAFLD], chronic alcohol consumption, non-alcoholic steatohepatitis [NASH], advanced age) will have abdominal ultrasound screenings and be monitored regularly (e.g., annually) for alpha-fetoprotein (AFP) elevations for 5 years following administration. <p>Renewal Criteria</p> <ul style="list-style-type: none"> ▪ Coverage cannot be renewed.
Quantity Limit	1 kit x 1 dose
Duration of Approval	Initial: One dose Renewal: N/A
Drug to Disease Hard Edit	None

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