



Hemophilia Agents

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Factor VIII Products

Drug	Manufacturer	Indications
antihemophilic factor VIII - recombinant (Advate®) ¹	Baxter Healthcare	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 adults and children with hemophilia A
antihemophilic factor VIII – plasma derived (Alphanate®) ²	Grifols Biologics	Control and prevention of bleeding episodes in adults and children with hemophilia A Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand’s disease (vWD) in whom desmopressin is ineffective or contraindicated; it is not indicated for patients with severe vWD undergoing major surgery
antihemophilic factor VIII – recombinant (Helixate FS®) ³	Bayer Healthcare (distributed by CSL Behring)	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 adults and children with hemophilia A with no preexisting joint damage
antihemophilic factor VIII – plasma derived (Hemofil M®) ⁴	Baxter Healthcare	Control and prevention of hemorrhagic episodes in (classical hemophilia) hemophilia A Not indicated for vWD
antihemophilic factor VIII – plasma derived (Humate-P®) ⁵	CSL Behring	Treatment and prevention of bleeding in adults with hemophilia A (classical hemophilia) 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 – plasma derived (Koate DVI®) ⁶	Grifols Therapeutics (distributed by Kendrion Biopharma)	Treatment of hemophilia A (classical hemophilia) in which there is a demonstrated deficiency of activity of the plasma clotting Factor VIII to control or prevent bleeding episodes, or in order to perform emergency and elective surgery on individuals with hemophilia. Not approved for use in vWD
antihemophilic factor VIII – recombinant (Kogenate FS®) ^{7,8}	Bayer Healthcare	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 adults and children with hemophilia A with no preexisting joint damage

Factor VIII Products (continued)

Drug	Manufacturer	Indications
antihemophilic factor VIII – plasma derived (Monoclate-P®) ⁹	CSL Behring	Treatment of (classical hemophilia) hemophilia A
antihemophilic factor VIII – recombinant (Recombinate®) ¹⁰	Baxter Healthcare	Control and prevention of hemorrhagic episodes in (classical hemophilia) hemophilia A Perioperative management in patients with hemophilia A Not indicated for vWD
antihemophilic factor VIII – plasma derived (Wilate®) ¹¹	Octapharma USA	Treatment of spontaneous and trauma-induced bleeding episodes in patients with vWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated Not indicated for treatment of hemophilia A
antihemophilic factor VIII – recombinant (Xyntha®) ^{12,13}	Wyeth Pharmaceuticals	Control and prevention of bleeding episodes in patients with hemophilia A (congenital Factor VIII deficiency or classic hemophilia) Surgical prophylaxis in patients with hemophilia A

Factor IX Products

Drug	Manufacturer	Indications
coagulation factor IX – plasma derived (AlphaNine SD®) ¹⁴	Grifols Biologics	Indicated for the prevention and control of bleeding in patients with Factor IX deficiency due to hemophilia B AlphaNine SD contains low, non-therapeutic levels of Factors II, VII, and X, and is not indicated for the treatment of Factor II, VII or X deficiencies Not indicated for the treatment of hemophilia A patients with inhibitors to Factor VIII
coagulation factor IX – plasma derived (Bebulin®/Bebulin VH®*) ¹⁵	Baxter Healthcare	Indicated for the prevention and control of hemorrhagic episodes in hemophilia B patients; it is not indicated for use in the treatment of Factor VII deficiency; no clinical studies have been conducted to show benefit from this product for treating deficiencies other than Factor IX deficiency
coagulation factor IX – recombinant (BeneFIX®) ¹⁶	Wyeth Pharmaceuticals	Indicated for the prevention and control of bleeding episodes in adults and pediatric patients with hemophilia B Indicated for peri-operative management in adults and pediatric patients with hemophilia B Not indicated for the treatment of other factor deficiencies (e.g., Factors II, VII, VIII and X), or the treatment of hemophilia A patients with inhibitors to Factor VIII
coagulation factor IX – plasma derived (Mononine®) ¹⁷	CSL Behring	Prevention and control of bleeding in Factor IX deficiency, also known as hemophilia B Not indicated in the treatment or prophylaxis of hemophilia A in patients with inhibitors to Factor VIII Mononine contains non-detectable levels of Factors II, VII, and X and is, therefore, not indicated for replacement therapy of these clotting factors

Factor IX Products (continued)

Drug	Manufacturer	Indications
coagulation factor IX – plasma derived (Profilnine SD®) ¹⁸	Grifols Biologics	Indicated for the 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

*Bebulin VH is in the process of being phased out in favor of Bebulin.

Factor VII Products

Drug	Manufacturer	Indications
coagulation factor VII – plasma derived (Feiba NF) ¹⁹	Baxter Healthcare	Indicated for the control of spontaneous bleeding episodes or to cover surgical interventions in hemophilia A and hemophilia B patients with inhibitors
coagulation factor VII - recombinant (Novo Seven RT) ²⁰	Novo Nordisk	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 (FVII) Deficiency Prevention of bleeding in surgical interventions or invasive procedures in congenital FVII deficiency

OVERVIEW^{21,22,23}

Hemophilia is a rare, inherited bleeding disorder where the blood does not clot properly caused by an absence in one of the coagulation factors present in normal blood. Hemophilia is identified as an X-linked congenital bleeding disorder that has an estimated frequency of one in ten thousand births. The World Foundation of Hemophilia estimates the global prevalence of hemophilia at around 400,000 persons. It is estimated there are approximately 17,000-20,000 persons in the United States afflicted with hemophilia.

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 two 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 percent of all 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 percent 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 VII or factor IX, in the patient's blood. The following table details the severity, general clotting factor level and bleeding episode characteristics for hemophilia.

Severity	Level of Clotting Factor	Bleeding Characteristics
Mild hemophilia	5% to less than 40% of normal (5-40 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 (1-5 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	Less than 1% of normal (less than 1 IU/dL)	Patient can experience spontaneous bleeds without injury; joint and muscle bleeds are common; may experience bleeds one to two times a week

Bleeding into joints or hemarthrosis is more common than bleeds into muscles, the central nervous system or other major bleeds and comprise between 70 percent to 80 percent 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.

In July 2012 the World Federation of Hemophilia published its comprehensive treatment guidelines for the disease. The guidelines list the general principles of care for treatment of bleeding episodes. These include the prevention and treatment of bleeds with the specific factor concentrate for that patient's clotting deficiency; treatment of active bleeds as soon as possible and preferably within a two hour window of onset; help in teaching patients to recognize a bleeding aura which is often experienced prior to outward evidence of a bleed; the use of adjunctive therapies to help control bleeds including compression and cold therapy; ensuring that patients seek experienced medical care, including a pediatric or adult hematologist and continuing care through a recognized hemophilia treatment center; use of patient training and home therapy to treat non-life threatening bleeding episodes; comprehensive care plans that encourage and promote regular exercise to improve overall fitness while avoiding activities likely to cause trauma; maintaining good oral health and regular appointments to monitor health status.

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

Von Willebrand's disease (vWD) is related to hemophilia A and is a group of inherited bleeding disorders related to defects of von Willebrand's Factor, which is needed to achieve hemostasis. Von Willebrand's factor includes factor VIII. 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 one in 100 to 10,000 individuals, but is noted to be higher in patients with type O blood. Pregnancy can increase vWF levels and make diagnosis difficult. There are three major subtypes of vWD identified. Type 1 is a partial quantitative deficiency of vWF deficiency and accounts for 75 percent of all patients. Type 2 is a more pronounced qualitative deficiency and comprises almost all the remaining 25 percent of patients. Type 3 is characterized as a complete vWF deficiency and occurs very rarely. Type 2 disease is further divided into four 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's syndrome may also occur, but is highly rare, occurring in fewer than one in 100,000 adults. Three main approaches for the treatment of vWD are used and include increasing plasma concentrations of vWF through stimulation with desmopressin (DDAVP); replacing vWF by using human plasma-derived viral inactivated concentrates; and promoting hemostasis by utilizing hemostatic agents with mechanisms other than increasing vWF. Regular prophylaxis for von Willebrand's patients is seldom required.

PHARMACOLOGY^{24,25,26,27,28,29,30}

Factor VIII and IX, along with factor VII 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, Helixate FS, Kogenate FS, Recombinate, and Xyntha. Kogenate FS and Helixate FS are both manufactured by Bayer Corporation who markets the recombinant factor VIII product as Kogenate FS while CSL Behring distributes the product as Helixate FS. Since Recombinate contains 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. Helixate FS and Kogenate FS, 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. Advate and Xyntha are considered third-generation factor VIII products due to the fact they do not contain any animal or human plasma-derived proteins in either the culture medium or final formulation. 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 products biological activity.

Pooled, human plasma-derived factor VIII products for the treatment of hemophilia A include Alphanate, Hemofil M, Humate-P, Koate-DVI, Monoclate-P and Wilate. With the exception of Wilate, the products are indicated for use in hemophilia A. Wilate is only indicated for patients with vWD but does contain and although Wilate is not indicated in hemophilia A, it does contain Factor VIII. Then 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 both products may be used to treat vWD patients, they are not identical and should not be regarded as interchangeable.

When considering factor IX products for the treatment of hemophilia B, BeneFIX is the sole product made by recombinant technology; all of the other products are derived from human plasma. Additionally, the BeneFIX manufacturing process does not use any human or animal proteins making the risk of human blood-borne viral contamination extremely low. AlphaNine SD and Mononine are human plasma-derived products that are considered to be of high purity in comparison to other plasma-derived factor IX agents employing added and improved methods of screening and viral depletion. While these additional methods serve to reduce the risk, there does remain the slight possibility of viral transmission. Transmission of human parvovirus B19 and hepatitis A have occurred, however, the risk has been reduced with the use of additional viral attenuation methods such as ultrafiltration. Bebulin and Profilnine SD are also human plasma-derived products considered to be of lower purity. One of these product variations, Bebulin VH is being phased out in favor of Bebulin, which employs nanofiltration in addition to vapor heat for the purification process. These last two products are also referred to as Prothrombin Complex Concentrates (PCCs) as they contain detectable levels of other clotting factors including factors II, VII, IX, and X. Bebulin and Profilnine SD can, in some instances be used to treat patients with deficiencies of Factors II and X but they vary significantly in the amounts of factors that they contain. Further complicating the additional use is the fact there commonly may be a marked differences in factor content between the different lots of the same agent produced by the same manufacturer.

The National Hemophilia Foundation Medical and Safety Advisory Committee (MASAC) published revised recommendations regarding products used for the treatment of hemophilia and other bleeding disorders in May 2012. The recommendations state the risk of human viral contamination associated with recombinant factor VIII products is reduced in comparison with the risk with plasma-derived factor VIII products. There have been no reported instances of seroconversion of human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) with recombinant derived products. Recombinant factor VIII products are the recommended treatment of choice by MASAC for patients with hemophilia A. MASAC also recommended that manufacturers should work toward the removal of human albumin, as well as human and/or bovine proteins from their manufacturing processes for the recombinant factor VIII products.

The MASAC 2012 recommendations also addressed the use of plasma-derived factor VIII products. The MASAC recommendations stated improved purification and viral-depleting processes along with increased donor screening processes have greatly reduced the risk of transmission from plasma-derived factor products of HIV, HBV, and HCV. There have not been any reported instances of seroconversion of HIV, HBV, or HCV as a result of the use of any plasma-derived factor VIII products currently available in the United States. This includes products that undergo the following

purification/viral inactivation measures: heating in aqueous solution (pasteurization), solvent-detergent treatment, and/or immunoaffinity chromatography purification. Each of these methods whether employed alone or in conjunction with another process appears to have greatly reduced the risk of viral transmission compared to older methods. Despite the improvements and lack of any documented transmission, MASAC maintains there remains a possibility of HIV-1, HIV-2, HBV or HCV virus transmission with the use of currently marketed, viral-inactivated, plasma-derived products. The MASAC guidelines also caution that other non-lipid enveloped viruses may also be transmitted by plasma-derived factor VIII products. MASAC acknowledges that additional measures have been taken such as viral filtration to further reduce any potential transmission risks.

Similar to the recommendations for factor VIII products, MASAC stated that BeneFIX, a recombinant product, should 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 and may be considered the safest of the factor IX agents.

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

PHARMACOKINETICS

The pharmacokinetics of various factor products dosed on an episodic basis is generally stable, however, this can vary depending on individual patient characteristics and factors such as the presence of inhibitors.

CONTRAINDICATIONS/WARNINGS

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.

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

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

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).

DRUG INTERACTIONS

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.

ADVERSE EFFECTS^{31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51}

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 Concentrates (PCCs), Bebulin and Profilnine SD, that contain significant amounts of activated Factors VII, X, and prothrombin. While the risk may be increased with

plasma-derived products, BeneFIX, the only recombinant factor IX product has also been associated with the development of thromboembolic complications.

All factor products, factor VIII, factor IX and factor VII, 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.

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

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

In situations where a patient who has previously responded positively to factor infusion therapy fails to respond clinically to clotting factors, the presence of inhibitors should be suspected and appropriate testing performed. In situations where inhibitors are present, the expected response, clinical effect and half-life of the transfused clotting factor are severely compromised.

Inhibitors are more frequently encountered in persons with severe hemophilia in comparison to patients diagnosed those 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 percent and 30 percent. The risk is significantly lower for patients diagnosed with mild to moderate hemophilia falling between five percent to 10 percent over a lifetime. Finally, the prevalence of inhibitor development is much less frequent in hemophilia B than hemophilia A, occurring in less than five percent 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 in patients with severe hemophilia A is three 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 thirty 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 titre), should be performed in a qualified performed in the laboratory, preferably using the Nijmegen-modified Bethesda assay method. When the patients are children, screening for inhibitors should be performed once every five 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 review. If there is an instance of any failure to adequately respond to normal factor concentrate replacement dose in a patient who previously demonstrated a positive clinical response is an indication to assess for the emergence of an inhibitor.

Inhibitor measurement should also be done for all patients who have been intensively treated with factor therapy for more than five days duration, within four weeks of their last infusion should undergo inhibitor screening and measurement. Inhibitors should also 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 as assessment should be performed.

There are two 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 have 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 titre levels may drop or even become undetectable. Unfortunately, this effect is only temporary and there will be a recurrence anamnestic response along with a rise in the inhibitor titre level generally in three to five days following exposure to specific factor products. In contrast, certain low titre inhibitors may be transient and disappear commonly within six 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 titre 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.

SPECIAL POPULATIONS

Pediatrics

Please refer to the FDA-approved indications table.

Pregnancy

The factor VIII products Advate, Alphanate, Helixate FS, Hemofil M, Humate-P, Kogenate FS, Monoclate-P, Recombinate, Wilate and Xyntha all carry a pregnancy category designation C. Similarly,

factor IX products AlphaNine SD, Bebulin/Bebulin VH, BeneFIX, Mononine and Profilnine SD also carry a pregnancy category C. Feiba NF/Feiba VH and NovoSeven RT are also pregnancy category C.

Geriatrics

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

DOSAGES^{52,53,54,55,56,57,58,59,60,61,62}

There are two 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.

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

In 2007 the National Hemophilia Foundation Medical and Scientific Advisory Council, (MASAC), made recommendations regarding prophylaxis dosing, (regular administration of clotting factor concentrate to prevent bleeding). Because of the benefits demonstrated by prophylactic therapy, MASAC recommends that prophylaxis be considered optimal therapy for individuals with severe hemophilia A or B. Prophylaxis therapy should be initiated early, with the goal of keeping trough values for factor VIII or factor IX levels above one percent between doses, although benefit is still seen when trough levels fall below the target goal. This can usually be accomplished by following one of two commonly accepted prophylaxis protocols. The first is the Malmö protocol where 25-40 IU/kg per dose are administered three times per week for patients with hemophilia A or twice a week for patients with hemophilia B. The second is the Utrecht protocol where 15-30 IU/kg per dose are given three times per week for patients with hemophilia A or twice a week for patients with hemophilia B. Some variations of these dosing schedules call for every other day administration. Protocols should be individualized to the extent possible taking into account age, bleeding phenotype, activity, cost and factor availability. Individuals should have regular follow-up visits for evaluation of joint status. There are not specific guidelines regarding when to stop prophylaxis or at what age prophylaxis benefit decreases, although some data suggests that some young adults do well after prophylaxis has ended. Recombinant factors products are the most appropriate choice for prophylaxis because of markedly reduced risk of blood-borne infection, however as noted earlier there is data that suggests that plasma-derived factor VIII products may have a marginally reduced risk although the conclusion is not definitive. Potential reasons to discontinue prophylaxis include development of an inhibitor or patient preference (with physician agreement).

Episodic dosing is also often based on physician preference taking into account the patients severity, location and type of trauma. The goal of episodic treatment is to raise the factor level in the blood

from 40 percent to 100 percent 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. For hemophilia A patients a commonly accepted calculation is: patient weight pounds divided by 4.4 multiplied by the factor level or correction factor desired. The result is the number of factor VIII units required:

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

For hemophilia B patients a similar accepted calculation is: patient weight 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.⁶³ 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 that neutralize exogenous clotting factors. If a patient does not respond clinically to the usual dose of factor, which has previously been responsive, the development of an inhibitor must be suspected as these may be considered the most severe treatment related complication in hemophilia. In these cases, care must be coordinated with the expertise of a hematologist who specializes in bleeding disorders as well as a hemophilia treatment center.

There are three primary methodologies for the treatment of persons with inhibitors including: High-Dose Clotting Factor Concentrates; Bypassing Agents: Special blood products are used to treat bleeding in people with high titer inhibitors. They are called bypassing agents. 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 stop the inhibitor reaction from happening in 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 for many weeks or months.

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 titre 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 three to five 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 factor VII products, (Feiba NF, Novo Seven RT), or in some cases prothrombin complex concentrates (PCC), including the activated forms (APCC), may prove more successful. It has been shown that efficacy of two doses of factor VII and one dose of APCC for management of joint bleeding are essentially equivalent. As with all factor therapy, however, some patients may respond better to one 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 three times a week to 200 IU/kg daily was recently stopped due to safety concerns and interpretation of the data.

Overall, the response to ITI may be less favorable in patients with moderate/mild hemophilia and current experience with ITI for hemophilia B inhibitor patients is limited. The principles for treatment of hemophilia B inhibitor patients is similar, but rate of success has proven is much lower. There is a possibility of the development of nephrotic syndrome by hemophilia B patients who have a documented history of severe allergic reactions to factor IX and undertake ITI therapy. The resultant nephritic 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.

Factor VIII Products

Drug	Purification	Storage	Availability
antihemophilic factor VIII - recombinant (Advate®) ⁶⁴	Immunoaffinity chromatography (IC) and solvent/detergent (SD)	Up to 6 months but the temperature should not to exceed 30°C (86°F); 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 – plasma derived (Alphanate®) ⁶⁵	Affinity chromatography (AC), solvent/detergent (SD), and dry heat 72 hours at 80°C	Up to 2 months but the temperature should not to exceed 30°C (86°F)	Single-dose vials in strengths of 250 IU, 500 IU, 1,000 IU, and 1,500 IU

Factor VIII Products (continued)

Drug	Purification	Storage	Availability
antihemophilic factor VIII – recombinant (Helixate FS®) ⁶⁶	Immunoaffinity chromatography (IC) and solvent/detergent (SD)	Up to 12 months but the temperature should not to exceed 25°C (77°F)	Single-use glass vials in strengths of 250 IU, 500 IU, 1,000 IU, 2,000 IU, and 3,000 IU
antihemophilic factor VIII – plasma derived (Hemofil M®) ⁶⁷	Immunoaffinity chromatography (IC) and solvent/detergent (SD)	Based upon the bottle expiration date but the temperature should not to exceed 30°C (86°F)	Single-dose bottles in strengths of 250 IU, 500 IU, 1,000 IU, and 1,700 IU
antihemophilic factor VIII – plasma derived (Humate-P®) ⁶⁸	Pasteurization 10 hours at 60°C	Up to 24 months or the expiration date on the bottle but the temperature should not to exceed 25°C (77°F)	Single-dose vials in strengths of 250, 500 and 1,000 IU of Factor VIII/vial and 600, 1,200 and 2,400 IU vWF:RCo/vial
antihemophilic factor VIII – plasma derived (Koate DVI®) ⁶⁹	Solvent/detergent (SD) and dry heat 72 hours at 80°C	Up to 6 months but the temperature should not to exceed 30°C (86°F)	Single-dose bottles in strengths of 250 IU, 500 IU, and 1,000 IU
antihemophilic factor VIII – recombinant (Kogenate FS®) ^{70,71}	Immunoaffinity chromatography (IC) and solvent/detergent (SD)	Up to 12 months but the temperature should not to exceed 25°C (77°F)	Single-use glass vials in strengths of 250 IU, 500 IU, 1,000 IU, 2,000 IU, and 3,000 IU
antihemophilic factor VIII – plasma derived (Monoclate-P®) ⁷²	Immunoaffinity chromatography (IC) and pasteurization 10 hours at 60°C	Up to 6 months but the temperature should not to exceed 25°C (77°F)	Single-dose vials in strengths of 250 IU, 500 IU, 1,000 IU, and 1,500 IU
antihemophilic factor VIII – recombinant (Recombinate®) ⁷³	Immunoaffinity chromatography (IC)	Based upon the bottle expiration date but the temperature should not to exceed 30°C (86°F)	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 – plasma derived (Wilate®) ⁷⁴	Solvent/detergent (SD) and dry heat 2 hours at 100°C	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	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
antihemophilic factor VIII – recombinant (Xyntha®) ^{75,76}	Solvent/detergent (SD) and nanofiltration	Up to 3 months but the temperature should not to exceed 25°C (77°F)	Single-use vials and prefilled dual-chamber syringes (Solofuse) in strengths of 250 IU, 500 IU, 1,000 IU, and 2,000 IU. Solofuse is available in 3,000 IU

Factor IX Products

Drug	Purification	Storage	Availability
coagulation factor IX – plasma derived (AlphaNine SD®) ⁷⁷	Dual affinity chromatography (AC), solvent/detergent (SD), and nanofiltration	Store between 2°C to 8°C. 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 – plasma derived (Bebulin®/Bebulin VH®*) ⁷⁸	Nanofiltration (Bebulin) and vapor heat (Bebulin VH)	Store at a temperature between 36°F to 46°F	Single-dose vials contain 200 to 1,200 IU and diluent
coagulation factor IX – recombinant (BeneFIX®) ⁷⁹	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) for up to 6 months	Single-use vials contain 250 IU, 500 IU, 1,000 IU, 2,000 IU, and 3,000 IU with diluent
coagulation factor IX – plasma derived (Mononine®) ⁸⁰	Immunoaffinity chromatography (IC), sodium thiocyanate and ultrafiltration	Store between 2°C to 8°C. May store at room temperature not to exceed 25°C (77°F) for up to 1 month	Single-dose vials contain approximately 500 IU and 1,000 IU with diluent
coagulation factor IX – plasma derived (Profilnine SD®) ⁸¹	Solvent/detergent (SD)	Store between 2°C to 8°C. May store at room temperature not to exceed 30°C (86°F) for up to 3 month	Single-dose vials of 500 IU, 1,000 IU, and 1,500 IU

Factor VII Products

Drug	Purification	Storage	Availability
coagulation factor VII – plasma derived (Feiba NF) ⁸²	Nanofiltration and vapor heat	Store at room temperature not to exceed 25°C (77°F) up to the label expiration; do not freeze	Single-dose vials of 500 U, 1,000 U, and 2,500 U with diluent
coagulation factor VII – recombinant (Novo Seven RT) ⁸³	Immunoaffinity chromatography (IC)	Store between 2°C to 25°C (36°F to 77°F) up to the label expiration date; do not freeze	Single-dose vials of 1 mg, 2 mg, 5 mg and 8 mg with diluent

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 percent 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/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 conclusions regarding the comparative safety or efficacy can be made.

SUMMARY

There is little direct comparative data for both the factor VIII or the factor IX products. 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 percent when dosed according to the patient's requirements. Factor products 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/physician preference, vial size for dosing convenience, and product availability.

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