



PRODUCT PROFILER

Helixate[®] FS

Antihemophilic Factor [Recombinant],
Formulated with Sucrose

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THE PRODUCT PROFILER

The Product Profiler provides P&T committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The Profiler provides information about pharmacology, clinical studies and FDA-approved indications, safety, efficacy, acquisition costs, and other pharmacoeconomic variables, along with additional P&T committee considerations, in a convenient package. Articles are written by experts in the field.

ABOUT THE AUTHOR

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DISCLOSURES

Maxine S. Losseff and Alan Caspi, PhD, PharmD, MBA, both report that they have no financial arrangements or affiliations that might constitute a conflict of interest with respect to this publication. CSL Behring provided funding for this publication.



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Antihemophilic Factor [Recombinant], Formulated with Sucrose

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Helixate® FS

Antihemophilic Factor [Recombinant], Formulated with Sucrose

INTRODUCTION

This Product Profiler introduces health care professionals to Helixate® FS, recombinant antihemophilic factor VIII (rFVIII), formulated with sucrose. Helixate® FS is an FDA-approved treatment indicated for the management of bleeding associated with hemophilia A, including the control and prevention of bleeding episodes in adults and children 0 to 16 years, perioperative bleeding risk management in adults and children, and routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage in children with hemophilia A with no preexisting joint damage.

Helixate® FS is a lyophilized powder that, on reconstitution, yields a recombinant antihemophilic factor suspended in sucrose for intravenous (IV) administration. Clinical studies have shown Helixate® FS to be a safe and effective treatment for control of bleeding episodes, bleeding prophylaxis, and prevention of bleeding when administered prior to surgical procedures in patients with hemophilia A (Helixate® FS Prescribing Information 2009). Helixate® FS comes packaged with the Mix2Vial™ – a needle-free transfer device that offers convenience and increased safety – and a sterile water diluent vial.

The following text presents a brief overview of the epidemiology of hemophilia A, the role of FVIII in the coagulation cascade, the etiology and pathophysiology of hemophilia A, and current treatment options. Additionally, the evidence-based literature supporting the FDA-approved indication for the administration of rFVIII, formulated with sucrose in the management and prophylaxis of hemophilia A is discussed.

Disease Overview

Hemophilia A is a rare genetic disorder associated with absence, deficiency, or defect in the blood coagulation FVIII, leading to impairment of the coagulation cascade, difficult-to-control bleeding episodes, and both trauma-induced and spontaneous hemorrhages. Approximately 18,000 Americans have symptomatic hemophilia, and an estimated 400 infants are born with the disease each year (NHLBI 2009). Although predominantly a hereditary coagulation disorder, hemophilia A also may arise independent of family history: as much as one-third of cases of hemophilia have been estimated to occur as a result of an acquired mutation and not due to genetic predisposition (Hoyer 1994, NHLBI 2009).

Hemophilia A, also known as “classic hemophilia,” represents about 90% of all hemophilia cases and occurs among individuals of all racial groups and geographic

locations; however, the disease most commonly affects males (NHLBI 2009). Hemophilia B represents roughly 10% of cases and is defined by low levels of clotting factor IX (NHLBI 2009). Although clinically indistinguishable, the etiology and treatment of these two hemophilias are distinct, and the two diseases must be differentiated by specific factor assays (Bolton-Maggs 2003). Hemophilia A is an X-linked recessive genetic disorder with constant phenotypic expression in families (Husain 2009). The bleeding tendency in hemophilia A is dependent on the extent of FVIII defect or the degree of FVIII deficiency, which determine the classifications of mild, moderate, or severe disease (Husain 2009).

Treatments for hemophilia A have advanced greatly in the last four decades. The aim of treatment is to sufficiently increase FVIII levels in the circulation to promote clotting and prevent or halt spontaneous or procedural bleeding episodes. The development of factor concentrates in the 1960s allowed for easy access to high-volume factor concentrates and self-injections, without the need for storage under frozen conditions (Hoyer 1994). The high risk of transmission of viral infections from human plasma, however, soon became apparent. This risk led to development of viral-inactivated factor products and recombinant factor concentrates developed through DNA technology for improved safety and wider use. Furthermore, with the use of sucrose as a replacement for human albumin to stabilize the rFVIII protein in suspension, the risk of transfer of unwanted plasma constituents was further reduced and, with such safety advances, FVIII replacement therapy has become increasingly accepted.

The Factor VIII Protein

FVIII is a complex plasma glycoprotein consisting of 2,332 amino acid residues and plays a pivotal role as a cofactor in the intrinsic blood coagulation cascade (Fang 2007). The FVIII protein is made up of three types of domains: A domain, B domain, and C domain (Thompson 2003). The C domains of the FVIII protein participate in the characteristic binding of the nonactivated form of FVIII to von Willebrand factor (VWF), and the A domains each bind a single atom of copper (Thompson 2003). The B domain is not required for coagulation and most of it can be deleted without loss of anticoagulant activity, except for the sequence adhering B to A3, which contains a major VWF binding site (Thompson 2003).

FVIII is produced primarily in the liver, although kidney, sinusoidal endothelial cells, and lymphatic tissues have been shown to produce small amounts of FVIII as well,

and the normal physiologic level of FVIII in the circulation is 1 U/mL (Bolton-Maggs 2003, Klinge 2002). This large and highly unstable protein is preserved upon interaction with the VWF protein, and, in healthy individuals, approximately 95% of FVIII is bound to VWF in the circulation (Thompson 2003). This relationship serves to protect FVIII from proteolysis and ensure high concentrations of FVIII at sites of active hemostasis, and its association with VWF prolongs its short half-life to approximately 10 hours (Thompson 2003). The molar ratio of FVIII to VWF is approximately 1:50, and this ratio remains consistent over a wide range of VWF levels (Thompson 2003).

Hemostasis and the Role of Factor VIII

Normal blood coagulation involves a series of enzymatic reactions in which FVIII plays an essential role. The hemostatic activity of FVIII depends on its activation and inactivation via proteolytic cleavages modulated by thrombin and protein C (Fay 1993, Thompson 2003).

Clotting involves a series of reactions initiated when tissue trauma or injury causes release of tissue factor (TF) from the injured endothelium and collagen-rich subendothelium (Figure 1) (Hoffman 2001). During the *Initiation Phase* of coagulation, TF interacts with other coagulation factors to convert small amounts of prothrombin to thrombin, which commences the *Amplification Phase*. During amplification, trace amounts of thrombin can promote FVIII clotting activity, increasing the specific activity by as much as 50-fold (Hoffman 2001, Thompson 2003). On thrombin cleavage of the α_3 acidic peptide at the A3 amino terminus, a major VWF high-affinity binding site is eliminated and the activated enzyme (FVIIIa) dissociates

from VWF (Thompson 2003). FVIIIa serves as a cofactor to the serine protease FIXa during conversion of the zymogen FX to the activated enzyme (FXa). The FIXa/FVIIIa complex, known as the intrinsic tenase complex, markedly increases the catalytic efficiency of FIXa (Fang 2007, Thompson 2003). Activation of FX has been shown to be a crucial step in the *in vivo* process of coagulation (Thompson 2003).

The end point of the amplification phase of the coagulation pathway is the generation of a large thrombin burst (Hoffman 2001). In the *Propagation Phase* of the cascade, the thrombin burst catalyzes fibrin from fibrinogen, leading to the *Stabilization Phase*, at which time the cross-linking of fibrin fibers forms the net that stabilizes the platelet plug and renders the fibrin insoluble.

Etiology, Pathophysiology, and Natural History of Hemophilia A

Hemophilia A is marked by quantitative or qualitative defects of FVIII that contribute to failure of secondary hemostasis (Bolton-Maggs 2003). Since FVIII mediates a key step in progression of the coagulation cascade, any defect of concentration or functional activity will interfere with effective clotting. A number of genetic mutations in the FVIII gene have been linked to ineffective or insufficient FVIII production, and thus to inadequate cofactor activity and interruption of the coagulation cascade (Bolton-Maggs 2003). In patients with hemophilia A, primary hemostasis, or formation of the platelet plug, occurs normally, but FVIII is not able to appropriately amplify FIXa activity in the conversion of FX to FXa. This leads to inadequate thrombin production and impaired development of the fibrin net needed to stabilize the plug

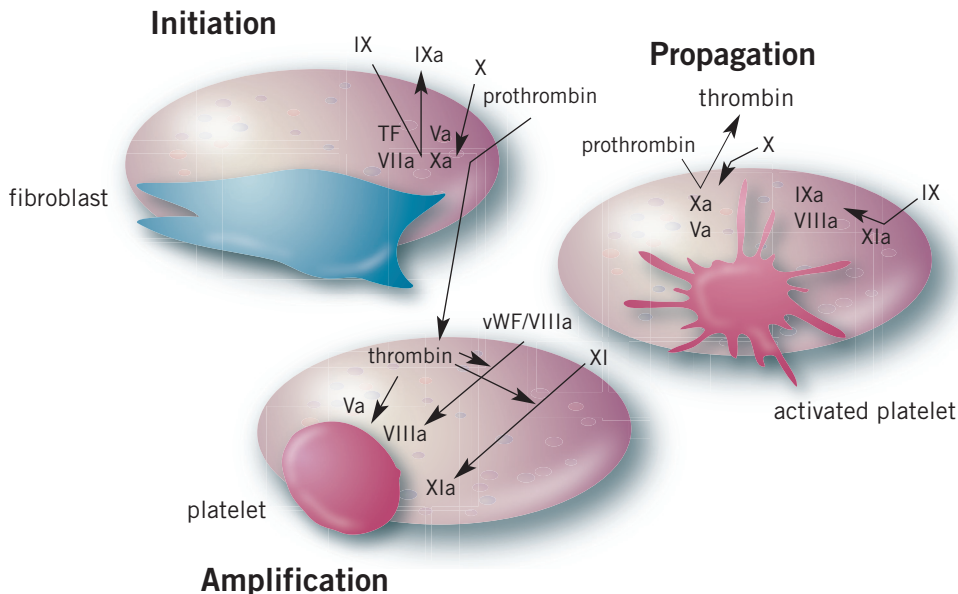


FIGURE 1
Cell-Based Model of Coagulation.
 Source: Adapted from Hoffman 2001.

(Bolton-Maggs 2003).

The severity of hemophilia A is determined by plasma levels in individuals with FVIII impairment. Mild disease defines those patients with $\geq 5\%$ to $\leq 40\%$ of normal factor levels, moderate disease ranges from 1% to 5% of normal levels, and severe disease includes individuals with $< 1\%$ of normal levels (Bolton-Maggs 2003). These categories can be used to predict bleeding risk, predict outcome, and guide management (Bolton-Maggs 2003). Clinical measures of frequency and severity of bleeding episodes are used as supplemental criteria for classification because, in some cases, patients will exhibit bleeding symptoms inconsistent with their procoagulant classification. For example, some patients may experience infrequent or mild bleeding despite FVIII levels consistent with severe disease (Bolton-Maggs 2003).

A defining characteristic of uncontrolled hemophilia A is persistent bleeding into joints and muscles (Bolton-Maggs 2003). Severe hemophilia A often results in joint and muscle bleeds as early as infancy, and such bleeds can occur as frequently as weekly (Manco-Johnson 2007). The presence of blood irritates the synovial lining and recurrent bleeds can cause synovial hypertrophy that predisposes patients to persistent bleeding and progressive damage to cartilage and subcondral bone (Bolton-Maggs 2003). In untreated or inadequately treated patients, this progressive damage can lead to fixed flexion and other joint deformities, particularly of the knees, ankles, and elbows, with associated muscle wasting (Bolton-Maggs 2003). In severe cases, extensive muscle wasting may result in immobility and may necessitate the use of a wheelchair (Bolton-Maggs 2003). Additionally, central nervous system (CNS) bleeding, or bleeding into the brain, is a major cause of mortality in this group, and approximately 3.3% to 35% of all death in patients with hemophilia A is due to CNS bleeding (Klinge 2002).

A common complication and great concern in the treatment of hemophilia A is development of alloantibodies – or inhibitors – to FVIII concentrate treatments (Ananyeva 2004). In fact, approximately 40% of patients with severe hemophilia A will develop such antibodies (Kempton 2009). Inhibitors neutralize the hemostatic activity of FVIII concentrates and interfere with the intended activity of substitution therapy, significantly reducing treatment efficacy (Fang 2007).

Molecular Genetics of Hemophilia A

The defect in FVIII activity or production is the result of a variety of FVIII gene mutations. The FVIII gene, comprised of 26 exons, is located on the long arm of the X chromosome at Xq28 and spans an estimated 186 kb (Bolton-Maggs 2003).

Nearly 1,000 mutations have been identified in hemophilia A (Husain 2009). The most common genetic derangement is a large inversion and translocation of exons 1-22 away from exons 23-26. The genetic deviation

is believed to be due to an error of DNA replication during spermatogenesis and is therefore specific to the male rather than female germ line; it has been observed in about 45% of individuals with severe hemophilia A (Antonarakis 1995, Bhopale 2003, Bolton-Maggs 2003). Other gene disruptions, including deletions, insertions, and point mutations, are responsible for the remaining 55% of cases (Bhopale 2003).

Mutations of the FVIII gene lead to either production of dysfunctional proteins or impaired expression, secretion, or stability of FVIII in circulation (Fang 2007). In some cases, altered FVIII folding and intracellular processing leads to decreased secretion, while in others, FVIII activation may be slowed or altered (Fang 2007). Additionally, it has been found that reduced VWF binding leads to rapid clearance of FVIII (Fang 2007). With nearly 1,000 genetic mutations playing a role, the physiologic outcomes of an FVIII gene defect are widely variable (Fang 2007). Approximately 60% of patients with FVIII mutations exhibit severe hemophilia A while the rest develop mild or moderate forms of the disease (Bhopale 2003).

Diagnosis of Hemophilia A

Hemophilia A is usually recognized when a male patient presents with unusual bleeding patterns. Cases may be noted based on easy or excessive bruising when a child begins to walk or when the first teeth break through the gums. Most patients with severe hemophilia are identified within the first year of life due to evidence of bleeding such as soft tissue, joint, or circumcision (NHLBI 2009). Today, the standard of care is to start prophylactic treatment at or before the first joint bleed, which is usually before the age of 4. Mild-to-moderate cases may not be diagnosed until later in life, often based on a history of hemarthroses, prolonged bleeding during surgical or dental procedures, or a first major trauma that reveals impaired clotting (Bolton-Maggs 2003).

The most common sites of hemophilic bleeds are in joints, particularly the knees, elbows, and ankles (Manco-Johnson 2007). Acute hemarthrosis is often recognized by tightness in the joint and later by severe pain or swollen, tense, or hot joints (NHLBI 2009). Joint symptoms will usually resolve over several days to a week but subsequent acute synovitis predisposes the joint to further hemorrhages (Klinge 2002, NHLBI 2009). Depending on the frequency of bleeds, the patient may experience chronic arthropathy. Early factor replacement therapy has been shown to prevent or slow the development of such chronic joint disease (Klinge 2002).

Muscle hematomas have been reported in as much as 30% of bleeding episodes, and have been known to compress vital structures, potentially leading to serious complications (Klinge 2002). Iliopsoas muscle bleeds, for instance, have been associated with muscle dysfunction and neural sequelae (Klinge 2002). Gross hematuria

affects as much as 75% of patients with hemophilia A; renal bleeding may be painless but colic can occur if a clot develops in the ureter or renal pelvis (Klinge 2002). CNS bleeding may be the most life-threatening complication of the disease (Klinge 2002).

The two most common conditions to be differentiated from hemophilia A are hemophilia B and von Willebrand disease (Bolton-Maggs 2003). It is impossible to distinguish among these clotting disorders by clinical criteria; however specific laboratory factor analyses can identify which blood component is deficient in order to make a specific diagnosis (Bolton-Maggs 2003). A family history is often present but is not essential to the diagnosis as family history is absent in roughly 30% of patients (Bolton-Maggs 2003).

Plasma concentration of FVIII assayed against a normal plasma standard of 1 U/mL will indicate the relative percentage of activity compared with the standard (Klinge 2002). The results of this assay yield the hemophilia severity classification of mild, moderate, or severe (Bolton-Maggs 2003). Additional laboratory testing may include prothrombin time (PT) and partial thromboplastin time (PTT), and factor IX assays (Merck Manual 2009).

Management of Hemophilia A

While there is no cure for hemophilia A, early treatment of spontaneous and trauma- or surgery-related bleeds is essential (Bolton-Maggs 2003). Available therapies that can raise FVIII concentrations sufficiently to initiate clotting are used to control or prevent such bleeding episodes (Bolton-Maggs 2003). Furthermore, manufacturing advances and recombinant DNA technology have produced products of increased purity, absent of animal or human proteins, making for safe and desirable treatment for patients with hemophilia A (Bolton-Maggs 2003). These therapies have vastly improved outcomes for patients with hemophilia A by providing bleeding control while decreasing the risk of transmission of human or animal pathogens (Bolton-Maggs 2003).

There are two main approaches to factor replacement therapy: episodic (on-demand) treatment and prophylaxis (Bolton-Maggs 2003). Episodic treatment allows imme-

diate treatment in the event of an active bleeding episode. This is reserved primarily for individuals with mild or moderate forms of hemophilia A. Prophylaxis, on the other hand, involves the injection of replacement therapy to control or prevent bleeding in patients at high risk of chronic bleeding events (Bolton-Maggs 2003). Prophylaxis can be used as either a single-dose treatment prior to an anticipated bleeding episode (e.g., dental procedures or participation in sports) or as a regular injection to cover a defined period of time. It can also be used as long-term prophylaxis to prevent spontaneous hemarthrosis, thereby avoiding irreversible arthropathy and incapacitation (Bolton-Maggs 2003). Available data indicate that use of prophylactic FVIII therapy in patients with severe disease results in a significant reduction in bleeding episodes, less deterioration of joint scores, and prevention of arthropathy (Manco-Johnson 2007). It is clear that, in patients with severe disease, prophylaxis should begin at an early age – preferably before the first joint bleed – which can occur once the child starts walking or running (Manco-Johnson 2007). While prophylaxis may prevent chronic bleeds, it is important to note that patients receiving prophylaxis may also require episodic treatment for active bleeds.

Approximately 30% to 50% of individuals treated with FVIII replacement therapy will develop inhibitor antibodies to treatment (Bolton-Maggs 2003). Inhibitors can vary in scale from low-titer, which may be remedied with increased FVIII concentrates, to high-titer, which markedly decreases the efficacy of FVIII therapy (Bhopale 2003, Bolton-Maggs 2003). Patients with high-titer FVIII inhibitors who experience a severe hemorrhage may also need to receive IV administration of activated prothrombin complex concentrate (aPTC) or a bypassing agent such as recombinant activated FVIIa (Klinge 2002). Eradication of inhibitors is complex and may require immune tolerance induction (ITI), which requires daily infusion of high-dose FVIII and immunosuppressive drugs over several months to years (Bhopale 2003). The efficacy of ITI can range from 60% to 80% and incurs a high initial cost with ITI failure being defined as a lack of tolerance by 33 months (Bhopale 2003, Kempton 2009).

Treatment Options

Transfusion Therapy

The first treatments for hemophilia were attempted in the early 20th century and included transfusion of fresh blood or whole plasma to replace blood loss. However, challenges of large delivery volume and/or frozen storage requirements limited the value of these treatments. The development of pooled factor concentrates and cryoprecipitates enabled patient self-administration, replacing the need for transfusion in the hospital. But despite purification processing, cryoprecipitates continued to carry risk of infection (HIV: 1/1,000,000 donations; HCV: 1/900,000) (MASAC 190). Today, therefore, cryoprecipitates are not recommended for the treatment of patients with hemophilia A (MASAC 190).

Desmopressin

Desmopressin acetate is a synthetic hormone that can increase clotting capabilities in individuals with mild-to-moderate hemophilia A. Desmopressin is an analog of vasopressin, a naturally occurring hormone that promotes secretion of VWF, thus increasing FVIII survival via the VWF/FVIII complex (Ozgonenel 2007). Available in several formulations and strengths, desmopressin can be administered via IV or subcutaneous injection or as a nasal spray (Table 1).

Patients with severe hemophilia A, or FVIII activity <1%, are not candidates for desmopressin therapy; however, those classified as having mild disease may benefit from its use (Ozgonenel 2007). Desmopressin therapy is also not appropriate for children younger than 2 years, pregnant women, cases of severe trauma, or in patients with mild hemophilia A in whom desmopressin does not adequately elevate FVIII levels (MASAC 190).

Factor VIII Replacement Therapies

Plasma-derived FVIII concentrates are purified proteins collected from pooled human plasma. Early experience with transmission of lethal viruses, particularly human immunodeficiency virus (HIV), confounded the use of the concentrates (Klinge 2002). Advances in donor screening and viral depletion processes have led to a greatly reduced risk for viral transmission with contemporary concentrates (MASAC 190). Nonetheless, there remains a theoretical risk for transmission of HIV-1, HIV-2, or hepatitis B or C with the use of viral-inactivated, plasma-derived products (MASAC 190).

Recombinant FVIII (rFVIII) is produced readily in established hamster cell lines transfected with a human FVIII gene (MASAC 190). Recombinant factor VIII concentrates, not derived from human plasma, are considered safer than plasma-derived concentrates. First generation products, however, used bovine or human serum albumin in the cell culture medium or added human serum albumin as a stabilizer in the final formulation. Although the risk of disease transmission appeared very small, newer products were designed with improvements such as products that use human and/or animal proteins in the medium but they do not appear in the final formulation. Instead, these products stabilize the rFVIII molecule with sucrose rather than with human serum albumin (MASAC 190).

The risk of viral transmission with these products is lower than with plasma-derived concentrates. None of the currently available recombinant Factor VIII concentrates have been reported to transmit any animal or human viruses or prions, and as a result, recombinant FVIII is the recommended therapy for patients with hemo-

TABLE 1
Forms of Desmopressin Acetate Indicated for the Management of Bleeding Disorders

Name	Delivery system	Concentration	Indication
DDAVP ^{®a}	Injection	4 mcg/mL	Mild to moderate classic VWD (Type I) with FVIII levels >5% Hemophilia with FVIII coagulant activity levels >5% Antidiuretic replacement therapy in the management of central (cranial) diabetes insipidus and for the management of temporary polyuria and polydipsia following head trauma or surgery in the pituitary region
Stimate [®]	Nasal spray	1.5 mg/mL ^b	Mild to moderate classic VWD (Type I) with FVIII levels >5% ^b Hemophilia A with FVIII coagulant activity levels >5%

^aDDAVP is a trademark of Sanofi-Aventis. Generic forms of desmopressin acetate 0.004 mg/mL for injection exist.

^bStimate 1.5 mg/mL is a high-concentrate formulation of this product. A low-concentrate form is used to treat diabetes and bed wetting and is not indicated for VWD.

Sources: DDAVP[®] Prescribing Information 2007, Stimate[®] Prescribing Information 2009.

philia A by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) (MASAC 190).

Adjunctive Therapy

Adjunctive therapies are another viable option for those patients suffering from hemophilia A. Two such therapies include the use of aminocaproic acid and tranexamic acid.

Aminocaproic acid competitively binds lysine sites on plasminogen and plasmin, effectively blocking the interaction of plasmin and fibrin, resulting in fibrinolysis inhibition (Majerus 2006). While aminocaproic acid is a potent inhibitor of fibrinolysis, thrombi that form during drug treatment are not adequately lysed causing clot formation and subsequent obstruction (Majerus 2006).

Aminocaproic acid has been used successfully in patients with hemophilia to reduce bleeding after prostatic surgery or after dental tooth extractions (Majerus 2006).

Tranexamic acid is another antifibrinolytic agent that competitively inhibits the receptor sites of plasminogen similarly to aminocaproic acid (Cyklokapron Prescribing Information 2008). Tranexamic acid, however, has approximately 10 times more potency in vitro than aminocaproic acid and has no influence on platelet counts in concentrations up to 10 mg per mL of blood (Cyklokapron Prescribing Information 2008). Tranexamic acid is appropriate for short-term use in the reduction or prevention of hemorrhage and replacement therapy during and following dental tooth extractions (Cyklokapron Prescribing Information 2008).

Product Information

INDICATIONS AND USAGE

Helixate® FS is an antihemophilic factor that is indicated for the control and prevention of bleeding episodes in adults and children (0-16 years) with hemophilia A.

Helixate® FS is indicated for surgical prophylaxis in adults and children with hemophilia A.

Helixate® FS is indicated for routine prophylactic treatment to reduce the frequency of bleeding episodes and the risk of joint damage in children with no preexisting joint damage.

Helixate® FS is not indicated for the treatment of von Willebrand's disease.

DESCRIPTION

Helixate® FS Antihemophilic Factor (Recombinant) is a coagulation factor VIII produced by recombinant DNA technology. It is produced by Baby Hamster Kidney (BHK) cells into which the human factor VIII gene has been introduced. The cell culture medium contains Human Plasma Protein Solution (HPPS) and recombinant insulin, but does not contain any proteins derived from animal sources. Helixate® FS is a purified glycoprotein consisting of multiple peptides including an 80 kD and various extensions of the 90 kD subunit. It has the same biological activity as factor VIII derived from human plasma. No human or animal proteins, such as albumin, are added during the purification and formulation processes of Helixate® FS.

The purification process includes a solvent/detergent virus inactivation step in addition to the use of the purification methods of ion exchange chromatography, monoclonal antibody immunoaffinity chromatography, along with other chromatographic steps designed to purify recombinant factor VIII and remove contaminating substances. Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents. Several of the individual production and raw material preparation steps in the Helixate®

Stabilizer	250 IU, 500 IU, 1000 IU	2000 IU, 3000 IU
Sucrose	0.9 – 1.3%	0.9 – 1.2%
Glycine	21 – 25 mg/mL	20 – 24 mg/mL
Histidine	18 – 23 mmol/L	17 – 22 mmol/L

Source: Helixate® FS Prescribing Information 2009.

FS manufacturing process have been shown to decrease TSE infectivity of that experimental model agent. TSE reduction steps include the Fraction II+III separation step for HPPS (6.0 log₁₀) and an anion exchange chromatography step (3.6 log₁₀).

Helixate® FS is formulated with the following as stabilizers (Table 2) in the final container and is then lyophilized. The final product is a sterile, nonpyrogenic, preservative-free, powder preparation for IV injection. IV administration of sucrose contained in Helixate® FS will not affect blood glucose levels.

The inactive ingredients/excipients listed in Table 3 are also contained in the final product.

CLINICAL PHARMACOLOGY

Helixate® FS temporarily replaces the missing clotting factor VIII that is needed for effective hemostasis.

The activated partial thromboplastin time (aPTT) is prolonged in patients with hemophilia. Determination of aPTT is a conventional in vitro assay for biological activity of factor VIII. Treatment with Helixate® FS normalizes the aPTT over the effective dosing period.

The pharmacokinetic properties of Helixate® FS were investigated in two separate studies in previously treated patients, adults, and children. Pharmacokinetic studies with Helixate® FS were conducted in 20 PTPs (ages 12 to 33 years) with severe hemophilia A in North America. The pharmacokinetic parameters for Helixate® FS were measured in a randomized, crossover clinical trial with the predecessor HELIXATE product with a single-dose administration of 50 IU/kg. After 24 weeks, the same dose of Helixate® FS was administered to the same patients. The recovery and half-life data for Helixate® FS were

Inactive Ingredient/ Excipient	250 IU, 500 IU, 1000 IU	2000 IU, 3000 IU
Sodium	27 – 36 mEq/L	26 – 34 mEq/L
Calcium	2.0 – 3.0 mmol/L	1.9 – 2.9 mmol/L
Chloride	32 – 40 mEq/L	31 – 38 mEq/L
Polysorbate 80	64 – 96 g/mL	64 – 96 g/mL
Sucrose	28 mg/vial	52 mg/vial
Imidazole, tri-n-butyl phosphate, and copper	Trace amounts	Trace amounts

Source: Helixate® FS Prescribing Information 2009.

unchanged after 24 weeks of continued treatment with sustained efficacy and no evidence of factor VIII inhibition (Table 4).

The pharmacokinetics of Helixate® FS were investigated in pediatric PTPs (4.4-18.1 years of age, average age 12). The pharmacokinetic parameters in children compared to adults show differences in higher clearance, lower incremental in vivo factor VIII recovery, and a shorter factor VIII half-life. This might be explained by differences in body composition such as body surface area and plasma volume. The pharmacokinetic parameters are depicted in Table 5.

TABLE 4
Pharmacokinetic Parameters for Helixate® FS Compared to HELIXATE

Parameter	Helixate FS®		HELIXATE
	Initial PK Mean (±SD)	PK at week 24 Mean (±SD)	Reference Mean (±SD)
AUC (IU • h/dL)	1588.05 ± 344.32	1487.08 ± 381.73	1879.02 ± 412.32
Cmax (IU/dL)	114.95 ± 20.19	109.42 ± 20.09	127.40 ± 33.21
Half-life (hr)	13.74 ± 1.82	14.60 ± 4.38	14.07 ± 2.62
In Vivo Recovery (IU/dL / IU/kg)	2.20 ± 0.34	2.11 ± 0.37	2.43 ± 0.60

Source: Helixate® FS Prescribing Information 2009.

TABLE 5
Pharmacokinetic Parameters for Helixate® FS in Children

Parameter	Mean (range)
AUC (IU • h/dL)	1320.0
Clearance (mL/h•kg)	4.1
Half-life (hr)	10.7 (7.8 – 15.3)
In Vivo Recovery (IU/dL /IU/kg)	1.9 (1.25 – 2.76)

Source: Helixate® FS Prescribing Information 2009.

Key Published Clinical Trials

A number of trials have followed the natural history of hemophilia A and evaluated the efficacy and safety of FVIII concentrates in controlling bleeding episodes and mitigating the progression of degenerative joint damage in patients with this condition. In one study, investigators evaluated the differential effects of long-term prophylaxis with rFVIII versus on-demand episodic therapy on the development of arthropathy when initiated in boys under 2 years of age with diagnosed hemophilia A (Manco-Johnson 2007). In two other studies, the safety and efficacy of a sucrose-formulated rFVIII-FS product were examined in comparison to earlier formulations that were produced with human albumin as a stabilizer, and its safety and efficacy were determined in previously treated adolescent/adult or treatment-naïve young (<4 years) males with severe hemophilia A.

Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia A

This study examined the question of whether episodic rFVIII therapy versus prophylactic infusions given every other day would yield better joint damage prevention in children with hemophilia A (Manco-Johnson 2007). In a multi-center, randomized, open-label trial, 65 boys under age 30 months with an FVIII activity level ≤ 2 U/dL were randomly assigned to either prophylaxis or episodic treatment. The prophylaxis group (n=32) received infusions of rFVIII at a dose of 25 IU/kg body weight every other day to prevent hemarthrosis — defined as acute episodes of joint pain with decreased joint motion. The group assigned to episodic treatment received rFVIII at a dose of 40 IU/kg at the time of joint hemorrhage. These children also received 20 IU at 24 and 72 hours later, continuing every other day until joint pain and mobility improved, for a maximum of 4 weeks.

The primary efficacy endpoint was preservation of index-joint structure as determined by magnetic resonance imaging (MRI) and plain film radiography. Secondary endpoints included number of joint and other bleeding events, number of infusions, and total units of rFVIII administered. Joint failure was defined as MRI or radiographic evidence of subchondral cyst, surface erosion, or joint-space narrowing. Early termination was allowed in the event of inhibitor development, life-threatening hemorrhage, or bone or cartilage damage seen on joint imaging. Children with inhibitory titers exceeding 25 Bethesda units (BU) in repeated sample testing or titers exceeding 10 BU for greater than 3 months were withdrawn from the study.

After a mean participation of 49 months, MRI findings

showed that all six index joints remained normal at 6 years of age in 93% of patients in the prophylaxis group compared with 55% in the episodic group ($P=.002$). This corresponded with an 83% reduction in risk of joint damage, based on MRI findings, associated with prophylactic versus episodic therapy. Radiographic findings were similar, revealing a substantial, if not statistically significant, difference in joint damage of 4% in the prophylaxis group versus 19% in the episodic group ($P=.10$). Mean joint and total hemorrhages annually were higher among boys receiving episodic therapy ($P<.001$). Serious adverse events are listed in Table 6.

Investigators concluded that prophylaxis with rFVIII is safe and effective in reducing the incidence of joint hemorrhages and life-threatening hemorrhages and in lowering the risk of joint damage among young boys with severe hemophilia A.

Sucrose Formulated Recombinant Human Antihe-mophilic Factor VIII is Safe and Efficacious for Treatment of Hemophilia A in Home Therapy

To evaluate the efficacy and safety of a new sucrose-formulated rFVIII product, investigators examined the bioequivalence of sucrose-formulated rFVIII against the established formulation in a randomized, crossover, open-label, pharmacokinetic study involving 35 subjects in Europe (EU) and North America (NA) (Abshire 2000). The study also determined the safety and efficacy of the new sucrose-based product when used for home therapy for up to 24 months in 71 subjects. The population included males ages 12 to 60 years with severe hemophilia A who were previously treated with a licensed FVIII concentrate. Patients with a history or current evidence of inhibitors to FVIII (≥ 0.6 BU) were excluded. The pharmacokinetic study (Stage I) was preceded by a 4- to 5-

TABLE 6
Serious Adverse Events

Event	Prophylaxis (n=32)	Episodic Therapy (n=33)
High-titer inhibitor (number of patients)	2*	0*
Life-threatening hemorrhage (number of patients)	0*	3*
Hemophilia-related hospitalization (mean number/patient/year)	1.70±8.03 [†]	0.47±0.85 [†]

* $P=.24$; [†] $P=.90$.
Source: Manco-Johnson 2007.

day washout after which subjects were randomly assigned to a 10-minute infusion of 50 IU/kg of one or the other product, and blood was drawn regularly over 48 hours for pharmacokinetic evaluation. After another 5-day washout period, subjects were crossed over to the other formulation and the testing was repeated. At 4 to 7 days after the second infusion, these individuals, along with 37 new subjects, continued into Stage II/III, which included 2 or 4 weeks of prophylaxis (20 IU/kg 3 times per week

by 10-minute infusion) in the EU or North America (NA) populations, respectively, followed by return to their pre-study episodic or prophylactic regimen. The primary efficacy endpoint was number of treatments per bleeding episode.

In Stage I, bioequivalence between rFVIII and rFVIII-FS was established, as measured by AUC_{NORM} , $C_{maxnorm}$, and $T_{1/2}$ across the two groups (Figure 2).

Nineteen NA subjects who continued into Phase II/III underwent ongoing pharmacokinetic evaluation to 24 weeks, which indicated that these pharmacokinetic measures remained consistent over the early home treatment period. Patients self-treating at home received a cumulative total of 12,546 infusions and 22,443,694 IU of rFVIII-FS. The 2,585 documented bleeds over the course of the study required 1 to 2 infusions to control bleeding in 93.5% of subjects; 80.5% of responses were deemed excellent or good. Adverse events described as at least remotely related to study drug included injection site reaction, rash, rash with pruritis, sweating, taste perversion, chest pain, diarrhea, hyperesthesia, hypertension, increased inhibitor titer, lipothymia, malaise, pruritis, rhinitis, seborrheic dermatitis increase, and stinging of the face. There was no evidence of *de novo* inhibitor formation over the course of the trial.

The authors of the study concluded that sucrose-formulated rFVIII-FS is safe and effective in providing desirable hemostatic activity for patients with severe hemophilia A. The product was well-tolerated with no *de novo* inhibitor formation or significant adverse events reported. Sucrose-formulated rFVIII-FS also offers an additional level of safety due to the lack of human-derived plasma proteins during formulation and purification.

Full-length Sucrose-formulated Recombinant Factor VIII for Treatment of Previously Untreated or Minimally Treated Young Children with Severe Haemophilia A

In this open-label, non-controlled trial, rFVIII-FS provided the sole source of FVIII replacement over the 2-year study period for 61 male children in EU and NA with severe hemophilia A (plasma FVIII <2%) who were ≤4 years of age. Study subjects were previously untreated (PUP, n=37) or minimally treated (MTP, n=24), defined as ≤4 exposure days (ED). MTPs were required to be negative for FVIII inhibitors (Bethesda assay <0.6 BU). Eligible subjects were enrolled in the study at the time they required FVIII replacement for their first on-study bleeding event. Treatment dose was 50 IU/kg body weight, rounded to the nearest whole vial amount, and administered by bolus infusion at a rate dependent on the individual patient's tolerance (usually <5 minutes). The primary efficacy endpoint was number of infusions needed to achieve hemostasis for each new bleeding episode.

The data revealed that of 1,178 bleeding episodes (41.7% mild, 47.3% moderate, and 7.7% severe), hemostasis was

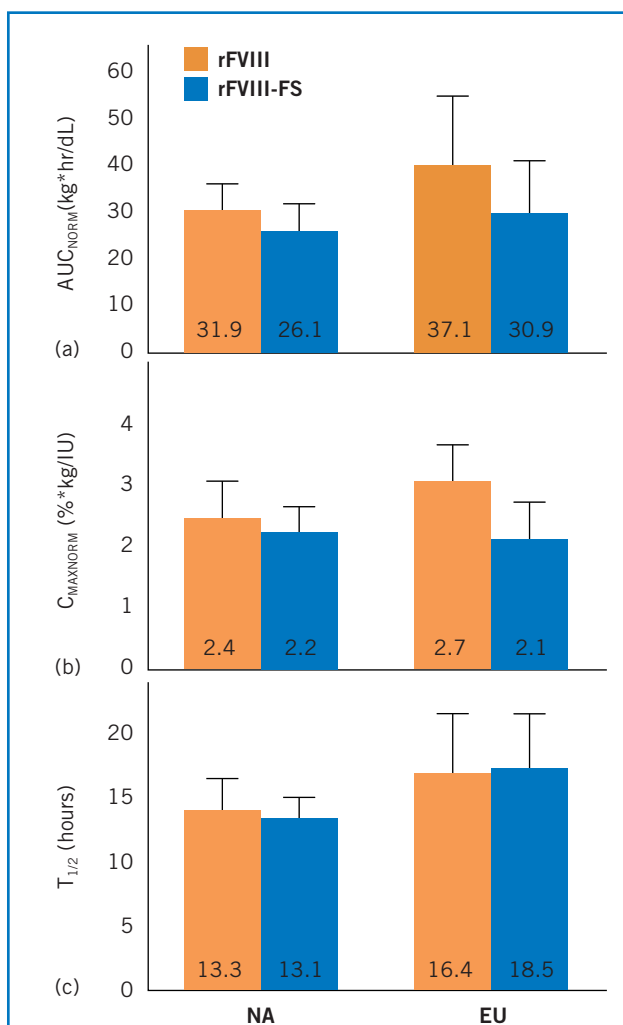
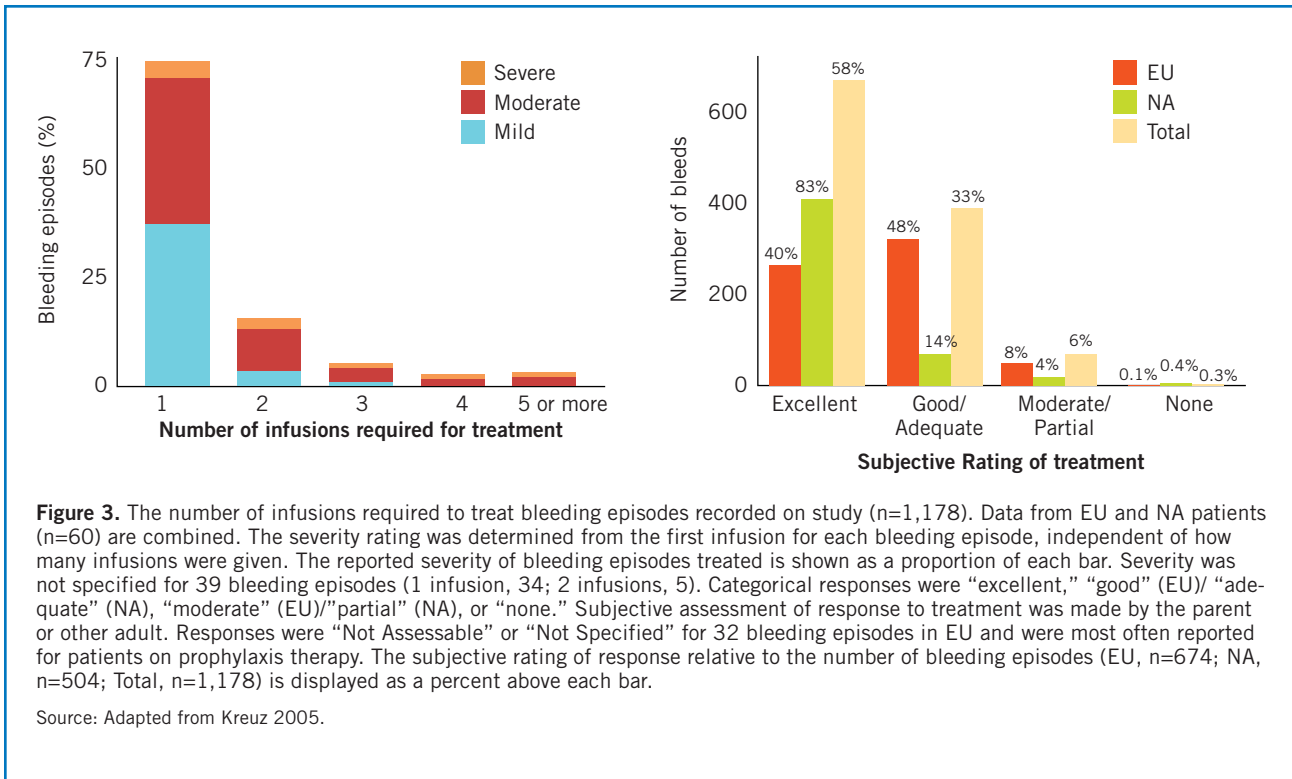


Figure 2. Pharmacokinetic parameters of rFVIII and rFVIII-FS were calculated using the 0-48 h interval. Bars show mean (SD ± error bars) and inset labels report median values of N patients (NA, 20; EU, 15). Bioequivalence was observed for the NA data, as the 90% confidence intervals (CI) for the ratio of geometric means for the AUC_{NORM} (0.803-0.916), $C_{maxnorm}$ (0.849-0.983), and $T_{1/2}$ (0.906-1.011) were within the specified bioequivalence interval (0.80-1.25). For the EU data, rFVIII and rFVIII-FS (N = 15) were bioequivalent with respect to $T_{1/2}$ (CI, 0.926-1.152), but not AUC_{NORM} (CI, 0.688-0.781) and $C_{maxnorm}$ (CI, 0.669-0.768).

Source: Adapted from Abshire 2000.



achieved by 74% with a single infusion and 89.2% with two infusions (Figure 3). “Severe” bleeding episodes, furthermore, were controlled with one or two infusions in 68.1% of patients. No surgical complications occurred among 22 children undergoing 27 procedures (mainly catheter implantation) and no transfusions of blood or blood derivatives were required. FVIII antibody formation was noted in 9 of 60 (15%) subjects. Only 13 adverse events were considered possibly related to study drug,

and included 10 cases of inhibitor formation; the overall adverse event rate was 0.14%, or 1 in 723 infusions.

Investigators concluded that rFVIII-FS provided hemostatic efficacy in the episodic treatment of spontaneous bleeding episodes and prophylactic surgical setting. This clinical trial also demonstrated the safety of rFVIII-FS in young children with hemophilia A over a median of 887 days on study.

Safety

CONTRAINDICATIONS

Helixate® FS is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including mouse or hamster proteins.

WARNINGS AND PRECAUTIONS

The clinical response to Helixate® FS may vary. If bleeding is not controlled with the recommended dose, the plasma level of factor VIII should be determined and a sufficient dose of Helixate® FS should be administered to achieve a satisfactory clinical response. If the patient's plasma factor VIII level fails to increase as expected or if bleeding is not controlled after the expected dose, the presence of an inhibitor (neutralizing antibodies) should be suspected and appropriate testing performed (*see Monitoring Laboratory Tests*).

Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with Helixate® FS and have manifested as pruritus, rash, urticaria, hives, facial swelling, dizziness, hypotension, nausea, chest discomfort, cough, dyspnea, wheezing, flushing, discomfort (generalized), and fatigue. Discontinue Helixate® FS if symptoms occur and seek immediate emergency treatment.

Helixate® FS contains trace amounts of mouse immunoglobulin G (MuIgG) and hamster (BHK) proteins. Patients treated with this product may develop hypersensitivity to these nonhuman mammalian proteins.

Patients treated with antihemophilic factor (AHF) products should be carefully monitored for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported following administration of Helixate® FS predominantly in previously untreated patients. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures factor VIII inhibitor concentration should be performed (*see Monitoring Laboratory Tests*).

Monitoring Laboratory Tests:

- Monitor plasma factor VIII activity levels by the one-stage clotting assay to confirm the adequate factor VIII levels have been achieved and maintained, when clinically indicated (*see Dosage and Administration*).
- Monitor for development of factor VIII inhibitors. If expected factor VIII plasma levels are not attained, or if bleeding is not controlled with the expected dose of Helixate® FS, perform assay to determine if factor VIII inhibitor is present. Use BU to titer inhibitors.

- If the inhibitor is less than 10 BU per mL, the administration of additional Helixate® FS concentrate may neutralize the inhibitor, and may permit an appropriate hemostatic response.
- Adequate hemostasis may not be achieved if inhibitor titers are above 10 BU per mL. The inhibitor titer may rise following Helixate® FS infusion as a result of an anamnestic response to factor VIII. The treatment or prevention of bleeding in such patients requires the use of alternative therapeutic approaches and agents.

ADVERSE REACTIONS

The most serious adverse reactions are systemic hypersensitivity reactions including bronchospastic reactions and/or hypotension and anaphylaxis and the development of high-titer inhibitors necessitating alternative treatments to AHF. The most common adverse reactions observed in clinical trials (frequency $\geq 4\%$ of patients) are inhibitor formation in PUPs and MTPs, skin-related hypersensitivity reactions (e.g., rash, pruritus), infusion-site reactions (e.g., inflammation, pain), and central venous access device (CVAD) line-associated infections in patients requiring a CVAD for IV administration.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

Previously Treated Patients (PTPs)

During the clinical studies conducted in PTPs, 451 adverse events (irrespective of the relationship to the study drug) were reported in the course of 24,936 infusions (1.8%). Twenty-four of the 451 adverse events were assessed as related to Helixate® FS (0.1%). Adverse reactions reported by $\geq 4\%$ of the patients are listed in Table 7.

Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs)

In clinical studies with pediatric PUPs and MTPs, 726 adverse events were reported in the course of 9,389 infusions (7.7%). Twenty-nine of the 726 adverse events were assessed as related to Helixate® FS (0.3%). Adverse reactions reported by $\geq 4\%$ of the patients are listed in Table 8.

Minimally Treated Patients (MTPs) in the Joint Outcome Study

In the Joint Outcome Study in MTP pediatric patients treated with routine prophylaxis or episodic enhanced treatment for 5.5 years, 46 of the 65 randomized patients experienced adverse events over the study duration. Adverse events were not assessed for their relationship with Helixate® FS.

Immunogenicity

In clinical studies with 73 PTPs (defined as having more than 100 exposure days), one patient had a preexisting inhibitor. In the other 72 patients, followed over 4 years,

TABLE 7
Adverse Reactions (AR) in Previously Treated Patients (PTPs) with Frequency of ≥ 4%

MedDRA Primary SOC	Preferred Term	Total No. of Patients: 73 No. of Patients with AR (%)	Total No. of Infusions: 24,936 AR per Infusion (%)
Skin and Subcutaneous Tissue Disorders	Rash, pruritus	6 (8.2%)	0.02
General Disorders and Administration Site Conditions	Infusion site reactions	3 (4.1%)	0.01

Abbreviation: SOC, system organ class.
Source: Helixate® FS Prescribing Information 2009.

TABLE 8
Adverse Reactions (AR) in Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs) with Frequency of ≥4% (Age Range 2-27 months)

MedDRA Primary SOC	Preferred Term	Total No. of patients: 61 No. of Patients with AR (%)	Total No. of Infusions: 9,389 AR per Infusion (%)
Skin and Subcutaneous Tissue Disorders	Rash, pruritus, urticaria	10 (16.4)	0.01
Blood and Lymphatic System Disorders	Factor VIII inhibition	9 (15)*	N/A
General Disorders and Administration Site Conditions	Infusion-site reactions	4 (6.6)	0.04

Abbreviation: SOC, system organ class.
*Denominator for *de-novo* inhibitors is N=60, since one patient had a preexisting inhibitor.
Source: Helixate® FS Prescribing Information 2009.

TABLE 9
Adverse Events (AE) in MTPs in the Joint Outcome Study (Age Range 0-6 years)

MedDRA Primary SOC	Preferred Term	Total No. of Prophylaxis Arm Patients: 32 No. of Patients with AE (%)	Total No. of Enhanced Episodic Arm Patients: 33 No. of Patients with AE (%)
Surgical and Medical Procedures	Central venous catheterization, catheter removal	19 (59)	18* (55)
Infections and Infestations	Central line infection	6 (19)	6 (18)
General Disorders and Administration Site Conditions	Pyrexia	1 (3)	4 (12)

Abbreviation: SOC, system organ class.
*Three patients from the enhanced episodic arm had catheter removal.
Source: Helixate® FS Prescribing Information 2009.

no de-novo inhibitors were observed. In clinical studies with pediatric PUPs and MTPs, inhibitor development was observed in 9 out of 60 patients (15%), 6 were high titer (>5 BU) and 3 were low-titer inhibitors. Inhibitors were detected at a median number of 7 exposure days (range 2 to 16 exposure days).

In the Joint Outcome Study with Helixate® FS, de-novo inhibitor development was observed in 8 of 64 patients with negative baseline values (12.5%), 2 patients developed high titer (>5 BU) and were withdrawn from the study. Six patients developed low-titer inhibitors. Inhibitors were detected at a median number of 44 exposure days (range 5 to 151 exposure days).

Post-Marketing Experience

The following adverse reactions have been identified during post approval use of Helixate® FS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Among patients treated with Helixate® FS, cases of serious allergic/hypersensitivity reactions (which may include facial swelling, flushing, hives, blood pressure decrease, nausea, rash, restlessness, shortness of breath, tachycardia, tightness of the chest, tingling, urticaria, vomiting) have been reported, particularly in very young patients or patients who have previously reacted to other factor VIII concentrates. Table 10 represents the post-marketing adverse reactions as MedDRA Preferred Terms.

TABLE 10
Post-Marketing Experience

MedDRA Primary SOC	Preferred Term
Blood and Lymphatic System Disorders	FVIII inhibition
Skin and Subcutaneous Tissue Disorders	Pruritus, urticaria, rash
General Disorders and Administration Site Conditions	Infusion-site reaction
	Pyrexia
Immune System Disorders	Anaphylactic reaction, other hypersensitivity reactions

Abbreviation: SOC, system organ class.
Source: Helixate® FS Prescribing Information 2009.

DOSAGE AND ADMINISTRATION

For Intravenous Use After Reconstitution

- Treatment with Helixate® FS should be initiated under the supervision of a physician experienced in the treatment of hemophilia A.
- Each vial of Helixate® FS has the recombinant factor VIII (rFVIII) potency in international units stated on the label.
- Helixate® FS is supplied in single-use vials. Pharmacists should work with clinicians to achieve the appropriate dosage while minimizing product wastage.
- Dosage and duration of treatment depend on the severity of the factor VIII deficiency, the location and extent of bleeding, and the patient’s clinical condition. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes (Table 11 and Table 12).

The expected in vivo peak increase in factor VIII level expressed as IU/dL (or % normal) can be estimated using the following formulas:

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

OR

$$\text{IU/dL (or \% normal)} = \frac{\text{Total Dose (IU)}}{\text{body weight (kg)}} \times 2 \text{ [IU/dL]/[IU/kg]}$$

Examples (assuming patient’s baseline factor VIII level is <1% of normal):

1. A dose of 1,750 IU Helixate® FS administered to a 70

kg patient should be expected to result in a peak postinfusion factor VIII increase of $1750 \text{ IU} \times \{[2 \text{ IU/dL}]/[\text{IU/kg}]/[70 \text{ kg}]\} = 50 \text{ IU/dL}$ (50% of normal).

2. A peak level of 50% is required in a 15 kg child. In this situation, the appropriate dose would be: $50 \text{ IU/dL} / \{[2 \text{ IU/dL}]/[\text{IU/kg}]\} \times 15 \text{ kg} = 375 \text{ IU}$.

Doses administered should be titrated to the patient’s clinical response. Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses to Helixate® FS. Although the dose can be estimated by the calculations above, it is highly recommended that, whenever possible, appropriate laboratory tests including serial factor VIII activity assays be performed (see *Monitoring Laboratory Tests and Pharmacokinetics*).

Control and Prevention of Bleeding Episodes

The careful control of treatment dose is especially important in cases of life-threatening bleeding episodes or major surgery.

Table 11 can be used to guide dosing in bleeding episodes.

TABLE 11
Control and Prevention of Bleeding Episodes for Children and Adults

Type of Bleeding Episode	Factor VIII Level Required (IU/dL or % of normal)	Dosage and Frequency Necessary to Maintain the Therapeutic Plasma Level
Minor Early hemarthrosis, minor muscle, or oral bleeds.	20-40	10-20 IU per kg Repeat dose if there is evidence of further bleeding.
Moderate Bleeding into muscles, bleeding into the oral cavity, definite hemarthroses, and known trauma.	30-60	15-30 IU per kg Repeat dose every 12-24 hours until bleeding is resolved.
Major Gastrointestinal bleeding. Intracranial, intra-abdominal or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces, or iliopsoas sheath. Fractures. Head trauma.	80-100	Initial dose 40-50 IU per kg Repeat dose 20-25 IU per kg every 8-12 hours until bleeding is resolved.

Source: Helixate® FS Prescribing Information 2009.

Peri-operative Management

The careful control of treatment dose is especially important in cases of major surgery or life-threatening bleeding episodes.

Table 12 can be used to guide dosing in surgery.

TABLE 12
Peri-operative Management for Adults and Children

Type of Surgery	Factor VIII Level Required (IU/dL or % of normal)	Dosage and Frequency Necessary to Maintain the Therapeutic Plasma Level
Minor Including tooth extraction.	30–60	15-30 IU per kg Repeat dose every 12-24 hours until bleeding is resolved.
Major Examples include tonsillectomy, inguinal herniotomy, synovectomy, total knee replacement, craniotomy, osteosynthesis, and trauma.	100	Pre-operative dose 50 IU per kg Verify 100% activity prior to surgery. Repeat as necessary after 6 to 12 hours initially, and for 10 to 14 days until healing is complete.

Source: Helixate® FS Prescribing Information 2009.

Routine Prophylaxis in Children with No Pre-existing Joint Damage.

The recommended dose for routine prophylaxis is 25 IU/kg of body weight every other day.

Instructions for Use

Helixate® FS is administered by IV injection after reconstitution. Patients should follow the specific reconstitution and administration procedures provided by their physicians.

For instructions, patients should follow the recommendations in the FDA-Approved Patient Labeling.

Reconstitution, product administration, and handling of the administration set and needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs. Place needles in a sharps container after single use. Discard all equipment, including any reconstituted Helixate® FS product, in an appropriate container.

Preparation and Reconstitution

Please see Full Prescribing Information at the end of the Product Profiler for directions on reconstitution and administration.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Helixate® FS is available as a kit in the following single-use glass vial sizes (Table 13). A suitable volume of Sterile Water for Injection, USP and Mix2Vial™ filter transfer device are provided in the kit.

TABLE 13
Vial Sizes for Helixate® FS

NDC Number	Approximate FVIII Activity (IU)	Diluent (mL)
0053-8131-02	250	2.5
0053-8132-02	500	2.5
0053-8133-02	1000	2.5
0053-8134-02	2000	5.0
0053-8135-02	3000	5.0

Source: Helixate® FS Prescribing Information 2009.

Actual factor VIII activity in IU is stated on the label of each Helixate® FS vial.

Storage and Handling

Product as Packaged for Sale:

- Store Helixate® FS under refrigeration (2-8°C or 36-46°F).
- Storage of lyophilized powder at room temperature (up to 25°C or 77°F) for 3 months, such as in home treatment situations, may be done. If Helixate® FS is stored outside the refrigerator, please add the date removed from refrigeration and note a new expiry date on the carton and vial. The new expiry date should be 3 months from the date product is removed from the refrigerator, or the previously stamped expiry date, whichever is shorter.
- Do not return to the refrigerator once Helixate® FS is removed from refrigeration.
- Do not use Helixate® FS after the expiration date indicated on the vial.
- Do not freeze.
- Protect from extreme exposure to light and store the lyophilized powder in the carton prior to use.

Product After Reconstitution:

- Administer Helixate® FS within 3 hours after reconstitution.
- It is recommended to use the administration set provided.

P&T Committee Considerations

Hemophilia A is a rare condition defined by potentially life-threatening bleeding episodes and requires lifelong therapy. The genetic disease, most often diagnosed in young males, has a hereditary element; however, up to 30% of cases occur spontaneously, secondary to an acquired mutation (Hoyer 1994). The diagnosis of hemophilia A often raises concerns among caregivers since it was historically associated with a low life expectancy and crippling joint deformities (Klinge 2002). However, present-day technology has allowed for increased safety and purity of FVIII replacement therapies, leading to an increase in life expectancy from 7.8 years in 1939 to over 70 years in 2001 (Ikkala 1982, Plug 2006).

Current treatment options have improved the prognosis of hemophilia A, and appropriate, prompt treatment and individualized patient care are necessary for patients to thrive. In order to promote optimal care of hemophilia patients, the federal government has funded a network of approximately 135 Hemophilia Treatment Centers (HTC) nationwide (CDC 2009). These centers, equipped with specialized doctors, nurses, and mental health professionals, are designed to treat all aspects of hemophilia and prevent serious complications of the disease (CDC 2009). This patient-centric approach to hemophilia care has proven beneficial. A study of 3,000 people with hemophilia demonstrated that the use of an HTC resulted in 40% fewer hospitalizations due to bleeding complications (CDC 2009). Additionally, the same study reported that patients who used an HTC were 40% less likely to die from a hemophilia-related complication. Pharmacists can play a role in the management of hemophilia A by conducting drug utilization reviews to evaluate adherence to therapy. By promoting adherence, pharmacists can help patients manage their disorder and decrease the risk of bleeds.

Regardless of where hemophilia patients receive care, a large concern for patients and providers alike is the development of FVIII inhibitors. Nearly 40% of hemophilia patients treated with FVIII replacement therapy will develop inhibitors (Kempton 2009). Inhibitor levels can range from low to high titer, and inhibitors pose a great challenge to hemophilia control (Bolton-Maggs 2003). To overcome the neutralizing effects of inhibitors on FVIII therapy, multiple medications may be needed, including large amounts of FVIII products, activated prothrombin complex concentrate, and/or bypassing agents such as recombinant activated FVIIa (Klinge 2002). This need for polypharmacy may result in an increase in AEs for the patient (Klinge 2002) as well as an increased cost burden.

The cost of hemophilia is high, largely due to the cost of therapy (Gringeri 2003). Beginning prophylaxis with FVIII

at an early age is beneficial because it may prevent joint damage and the subsequent immobility caused by such damage (Roosendaal 2007). Since dosing is weight based, starting prophylactic treatment at an early age will require small amounts of FVIII due to the low body weight of younger patients. Additionally, early prophylaxis can preserve joint structure and function, and may lower health care costs in the long run (Roosendaal 2007). Due to these demonstrable benefits of prophylaxis, the Medical and Scientific Advisory Council of the National Hemophilia Foundation (MASAC) has recommended that prophylaxis be considered optimal therapy for those with severe hemophilia A (MASAC 190).

Helixate® FS is a recombinant antihemophilic factor indicated for the control and prevention of bleeding episodes in adults and children (0 to 16 years) with hemophilia A, surgical prophylaxis in adults and children with hemophilia A, and routine prophylaxis in children with hemophilia A with no preexisting joint damage (Helixate® FS Prescribing Information 2009). Helixate® FS has been proven safe and effective in the treatment and prevention of bleeding in hemophilia A patients (Abshire 2000, Kreuz 2005, Manco-Johnson 2007). Additionally, clinical data show a low rate of inhibitor development (15%) in PUPs and MTPs (Kreuz 2005). Helixate® FS is manufactured following a stringent purification process that includes a solvent/detergent virus inactivation step, ion exchange chromatography, monoclonal antibody immunoaffinity chromatography, and other chromatographic steps designed to purify rFVIII and remove contaminating substances (Helixate® FS Prescribing Information 2009).

In addition to the rigorous safety standards upheld by the manufacturers of Helixate® FS, there are programs provided by CSL Behring to help patients, providers, and caregivers manage the treatment of hemophilia A. For example, the HeliTraxSM System allows for a comprehensive view of a patient's progress, with young patients relaying information about bleeding events and their use of Helixate® FS to their HTC via handheld device or Web interface between office visits. The HeliTraxSM System, used in conjunction with Helixate® FS treatment, is designed to improve patient-caregiver communications and therapy management. Another program, www.HemophiliaMoms.com, is a Web site containing true accounts from mothers raising kids with hemophilia. This Web site is designed to provide caregivers of hemophilia patients with practical information to help them meet day-to-day challenges. The goal of such programs is to facilitate treatment of hemophilia A and assist patients with treatment needs to encourage compliance and optimal treatment outcomes.

Conclusion

Hemophilia A is a rare coagulation disorder that affects approximately 18,000 males in the United States (NHLBI 2009). An X-linked genetic disorder, hemophilia A results from defects in the quantity or quality of FVIII, which interferes with appropriate progression of the coagulation cascade (Bolton-Maggs 2003). Until the development of FVIII replacement therapies, affected children were at risk for a variety of hemorrhages, chronic and painful arthropathy, debilitating joint degeneration, reduced life expectancy, and death related to CNS bleeds. The development of FVIII concentrates has greatly improved the prognosis and quality of life associated with this potentially life-threatening disease.

FVIII replacement products have gone through many changes since the earliest days of blood transfusion and plasma-derived cryoprecipitates (MASAC 190). Progress in factor concentration techniques, product purification, viral inactivation, and reconstitution and delivery methods have made contemporary factor replacement products a safe and effective treatment to manage bleeding. The established efficacy and safety profile of Helixate® FS, with low inhibitor formation rate and proven benefit in reducing joint damage, help to make Helixate® FS a preferred choice for the prophylaxis and episodic control of bleeding in patients with hemophilia A.

Glossary of Abbreviations

AE	Adverse event
aPCC	Activated prothrombin complex concentrate
AUC _{norm}	Normalized area under the concentration-time curve
CNS	Central nervous system
DNA	Deoxyribonucleic acid
EU	European Union
FDA	U.S. Food and Drug Administration
FIX	Factor IX
FV	Factor V
FVIII	Factor VIII
fXa (or IX, VIII, VII)	Activated factor X, IX, VIII, VII
HIV	Human immunodeficiency virus
HCV	Hepatitis C virus
IgG	Immunoglobulin G
MASAC	Medical and Scientific Advisory Council of the National Hemophilia Foundation
MRI	Magnetic resonance imaging
MTP	Minimally treated patient
NHF	National Hemophilia Foundation
PTP	Previously treated patient
PUP	Previously untreated patient
rFVIII	Recombinant factor VIII
TF	Tissue factor
VWF	von Willebrand factor

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Helixate FS safely and effectively. See full prescribing information for Helixate FS.

Helixate® FS
(Antihemophilic Factor [Recombinant], Formulated with Sucrose)
For Intravenous Use, Lyophilized Powder for Reconstitution

Initial U.S. Approval: 1993

RECENT MAJOR CHANGES

Indications and Usage (1.3)

8/2009

INDICATIONS AND USAGE

Helixate FS is an Antihemophilic Factor (Recombinant) indicated for:

- Control and prevention of bleeding episodes in adults and children (0-16 years) with hemophilia A (1.1).
- Peri-operative management in adults and children with hemophilia A (1.2).
- Routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage in children with hemophilia A with no pre-existing joint damage (1.3).

DOSAGE AND ADMINISTRATION

For intravenous use only (2)

- Each vial of Helixate FS contains the labeled amount of recombinant factor VIII in international units (IU)

Control and prevention of bleeding episodes and peri-operative management (2):

- Dose (units) = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).
- Frequency of intravenous injection of the reconstituted product is determined by the type of bleeding episode and the recommendation of the treating physician (2.1, 2.2).

For routine prophylaxis in children with no pre-existing joint damage, the recommended dose is 25 IU/kg every other day (2.3).

DOSAGE FORMS AND STRENGTHS

Helixate FS powder is available as 250, 500, 1000, 2000, and 3000 IU in single-use vials (3).

CONTRAINDICATIONS

Do not use in patients who have manifested life-threatening immediate hypersensitivity

reactions, including anaphylaxis, to the product or its components, including mouse or hamster proteins (4).

WARNINGS AND PRECAUTIONS

- Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with Helixate FS should be discontinued, and emergency treatment should be sought. Patients may develop hypersensitivity to mouse or hamster protein, which is present in trace amounts in the product (5.2).
- Development of activity-neutralizing antibodies has been detected in patients receiving factor VIII-containing products. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures factor VIII inhibitor concentration should be performed (5.3).

ADVERSE REACTIONS

The most common adverse reactions observed in clinical trials (frequency \geq 4% of patients) are inhibitor formation in previously untreated and minimally treated patients (PUPs and MTPs), skin-associated hypersensitivity reactions (e.g., rash, pruritus, urticaria, infusion site reactions (e.g., inflammation, pain), and central venous access device (CVAD) line-associated infections.

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed (8.1).
- Pediatric Use: Higher factor VIII clearance has been described in children (4.4-16 years) compared to adults. Dose adjustment may be needed (8.4).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: August 2009

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FULL PRESCRIBING INFORMATION

Helixate® FS

Antihemophilic Factor (Recombinant)

Formulated with Sucrose

1 INDICATIONS AND USAGE

1.1 Control and Prevention of Bleeding Episodes

Helixate® FS is an antihemophilic factor that is indicated for the control and prevention of bleeding episodes in adults and children (0-16 years) with hemophilia A.

1.2 Peri-operative Management

Helixate FS is indicated for surgical prophylaxis in adults and children with hemophilia A.

1.3 Routine Prophylaxis in Children with Hemophilia A with No Pre-existing Joint Damage

Helixate FS is indicated for routine prophylactic treatment to reduce the frequency of bleeding episodes and the risk of joint damage in children with no pre-existing joint damage.

Helixate FS is not indicated for the treatment of von Willebrand's disease.

2 DOSAGE AND ADMINISTRATION

For Intravenous Use After Reconstitution

- Treatment with Helixate FS should be initiated under the supervision of a physician experienced in the treatment of hemophilia A.
- Each vial of Helixate FS has the recombinant factor VIII (rFVIII) potency in international units stated on the label.
- Dosage and duration of treatment depend on the severity of the factor VIII deficiency, the location and extent of bleeding, and the patient's clinical condition.¹ Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes (see Table 1 and Table 2).

The expected in vivo peak increase in factor VIII level expressed as IU/dL (or % normal) can be estimated using the following formulas:

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

OR

$$\text{IU/dL (or \% normal)} = \text{Total Dose (IU)/body weight (kg)} \times 2 \text{ [IU/dL]/[IU/kg]}$$

Examples (assuming patient's baseline factor VIII level is <1% of normal):

1. A dose of 1750 IU Helixate FS administered to a 70 kg patient should be expected to result in a peak post-infusion factor VIII increase of 1750 IU x [(2 IU/dL)/(IU/kg)]/[70 kg] = 50 IU/dL (50% of normal).
2. A peak level of 50% is required in a 15 kg child. In this situation, the appropriate dose would be: 50 IU/dL/[(2 IU/dL)/(IU/kg)] x 15 kg = 375 IU.

Doses administered should be titrated to the patient's clinical response. Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses to Helixate FS.^{2,3,4} Although the dose can be estimated by the calculations above, it is highly recommended that, whenever possible, appropriate laboratory tests including serial factor VIII activity assays be performed (see *Monitoring Laboratory Tests [5.4] and Pharmacokinetics [12.3]*).

2.1 Control and Prevention of Bleeding Episodes

The careful control of treatment dose is especially important in cases of life-threatening bleeding episodes or major surgery.

The following table can be used to guide dosing in bleeding episodes:

Table 1 Control and Prevention of Bleeding Episodes for Children and Adults

Type of Bleeding Episode	Factor VIII Level Required (IU/dL or % of normal)	Dosage and Frequency Necessary to Maintain the Therapeutic Plasma Level
Minor Early hemarthrosis, minor muscle or oral bleeds.	20-40	10-20 IU per kg Repeat dose if there is evidence of further bleeding.

Type of Bleeding Episode	Factor VIII Level Required (IU/dL or % of normal)	Dosage and Frequency Necessary to Maintain the Therapeutic Plasma Level
Moderate Bleeding into muscles, bleeding into the oral cavity, definite hemarthroses, and known trauma.	30-60	15-30 IU per kg Repeat dose every 12-24 hours until bleeding is resolved.
Major Gastrointestinal bleeding. Intracranial, intra-abdominal or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces, or iliopsoas sheath. Fractures. Head trauma.	80-100	Initial dose 40-50 IU per kg Repeat dose 20-25 IU per kg every 8-12 hours until bleeding is resolved.

2.2 Peri-operative Management

The careful control of treatment dose is especially important in cases of major surgery or life-threatening bleeding episodes.

The following table can be used to guide dosing in surgery:

Table 2 Peri-operative Management for Adults and Children

Type of Surgery	Factor VIII Level Required (IU/dL or % of normal)	Dosage and Frequency Necessary to Maintain the Therapeutic Plasma Level
Minor Including tooth extraction.	30-60	15-30 IU per kg Repeat dose every 12-24 hours until bleeding is resolved.
Major Examples include tonsillectomy, inguinal herniotomy, synovectomy, total knee replacement, craniotomy, osteosynthesis, and trauma.	100	Pre-operative dose 50 IU per kg Verify 100% activity prior to surgery. Repeat as necessary after 6 to 12 hours initially, and for 10 to 14 days until healing is complete.

2.3 Routine Prophylaxis in Children with No Pre-existing Joint Damage.

The recommended dose for routine prophylaxis is 25 IU/kg of body weight every other day.⁵

2.4 Instructions for Use

Helixate FS is administered by intravenous (IV) injection after reconstitution. Patients should follow the specific reconstitution and administration procedures provided by their physicians.



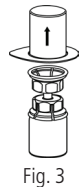
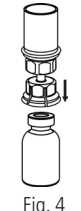

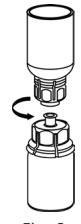
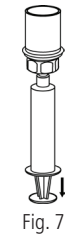
For instructions, patients should follow the recommendations in the FDA-Approved Patient Labeling (see *FDA-Approved Patient Labeling [17.1]*).

Reconstitution, product administration, and handling of the administration set and needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs. Place needles in a sharps container after single use. Discard all equipment, including any reconstituted Helixate FS product, in an appropriate container.

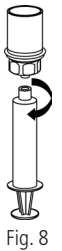
2.5 Preparation and Reconstitution

The procedures below are provided as general guidelines for the reconstitution and administration of Helixate FS. Always work on a clean flat surface and wash hands before performing the following procedures.

Vacuum Transfer and Reconstitution

1.	Warm the unopened diluent and the concentrate to a temperature not to exceed 37°C or 99°F.
2.	Place the product vial, diluent vial and Mix2Vial™ on a flat surface.
3.	Ensure product and diluent vial flip caps are removed and the stoppers are treated with an aseptic solution and allowed to dry prior to opening the Mix2Vial package.
4.	<p>Open the Mix2Vial package by peeling away the lid (Fig. 1). Leave the Mix2Vial in the clear package. Place the diluent vial on an even surface and hold the vial tight. Grip the Mix2Vial together with the package and snap the blue end onto the diluent stopper (Fig. 2).</p>  <p>Fig. 1</p>  <p>Fig. 2</p>
5.	<p>Carefully remove the clear package from the Mix2Vial set. Make sure that you only pull up the package and not the Mix2Vial set (Fig. 3).</p>  <p>Fig. 3</p>
6.	<p>With the product vial firmly on a surface, invert the diluent vial with the set attached and snap the transparent adapter onto the product vial stopper (Fig. 4). The diluent will automatically transfer into the product vial.</p>  <p>Fig. 4</p>
7.	<p>With the diluent and product vial still attached, gently swirl the product vial to ensure the powder is fully dissolved (Fig. 5). Do not shake vial.</p>  <p>Fig. 5</p>
8.	<p>With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the blue diluent-side of the Mix2Vial set and unscrew the set into two pieces (Fig. 6).</p>  <p>Fig. 6</p>
9.	<p>Draw air into an empty, sterile syringe. While the product vial is upright, screw the syringe to the Mix2Vial set. Inject air into the product vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly (Fig. 7).</p>  <p>Fig. 7</p>

10. Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the syringe plunger facing down) and unscrew the syringe from the Mix2Vial set (Fig. 8). Attach the syringe to an administration set made with microbore tubing. Use of other administration sets without microbore tubing may result in a larger retention of the solution within the administration set.



11. If the same patient is to receive more than one bottle, the contents of two bottles may be drawn into the same syringe through a separate unused Mix2Vial set before attaching the vein needle.

12. Helixate FS should be inspected visually for particulate matter and discoloration prior to administration.

2.6 Administration

For Intravenous Use Only After Reconstitution

- Helixate FS should be inspected visually for particulate matter and discoloration prior to administration. Turbid or discolored solution should be discarded.
- Reconstituted Helixate FS may be stored at room temperature prior to administration, but is to be administered within 3 hours.
- A dose of Helixate FS may be administered over a period of 1 to 15 minutes. The rate of administration however, should be adapted to the response of each individual patient. The pulse rate should be determined before and during administration of Helixate FS. If there is a significant increase in pulse rate, reducing the rate of administration or temporarily halting the injection allows the symptoms to disappear promptly.

3 DOSAGE FORMS AND STRENGTHS

Helixate FS is available as a lyophilized powder in single-use glass vials containing 250, 500, 1000, 2000, and 3000 International Units (IU).

Each vial of Helixate FS is labeled with the recombinant antihemophilic factor activity expressed in IU per vial. This potency assignment employs a factor VIII concentrate standard that is referenced to a WHO International Standard for factor VIII concentrates, and is evaluated by appropriate methodology to ensure accuracy of the results.

4 CONTRAINDICATIONS

Helixate FS is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including mouse or hamster proteins.

5 WARNINGS AND PRECAUTIONS

5.1 General

The clinical response to Helixate FS may vary. If bleeding is not controlled with the recommended dose, the plasma level of factor VIII should be determined and a sufficient dose of Helixate FS should be administered to achieve a satisfactory clinical response. If the patient's plasma factor VIII level fails to increase as expected or if bleeding is not controlled after the expected dose, the presence of an inhibitor (neutralizing antibodies) should be suspected and appropriate testing performed (*see Monitoring Laboratory Tests [5.4]*).

5.2 Anaphylaxis and Severe Hypersensitivity Reactions

Allergic-type hypersensitivity reactions including anaphylaxis have been reported with Helixate FS and have manifested as pruritus, rash, urticaria, hives, facial swelling, dizziness, hypotension, nausea, chest discomfort, cough, dyspnea, wheezing, flushing, discomfort (generalized) and fatigue. Discontinue Helixate FS if symptoms occur and seek immediate emergency treatment.

Helixate FS contains trace amounts of mouse immunoglobulin G (MuIgG) and hamster (BHK) proteins. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

5.3 Neutralizing Antibodies

Patients treated with antihemophilic factor (AHF) products should be carefully monitored for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests.⁶ Inhibitors have been reported following administration of Helixate FS predominantly in previously untreated patients. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures factor VIII inhibitor concentration should be performed (*see Monitoring Laboratory Tests [5.4]*).

5.4 Monitoring Laboratory Tests

- Monitor plasma factor VIII activity levels by the one-stage clotting assay to confirm the adequate factor VIII levels have been achieved and maintained, when clinically indicated (*see Dosage and Administration [2]*).
- Monitor for development of factor VIII inhibitors. If expected factor VIII plasma levels are not attained, or if bleeding is not controlled with the expected dose

of Helixate FS, perform assay to determine if factor VIII inhibitor is present. Use Bethesda Units (BU) to titer inhibitors.

- If the inhibitor is less than 10 BU per mL, the administration of additional Helixate FS concentrate may neutralize the inhibitor, and may permit an appropriate hemostatic response.
- Adequate hemostasis may not be achieved if Inhibitor titers are above 10 BU per mL. The inhibitor titer may rise following Helixate FS infusion as a result of an anamnestic response to factor VIII. The treatment or prevention of bleeding in such patients requires the use of alternative therapeutic approaches and agents.

6 ADVERSE REACTIONS

The most serious adverse reactions are systemic hypersensitivity reactions including bronchospastic reactions and/or hypotension and anaphylaxis and the development of high-titer inhibitors necessitating alternative treatments to AHF.

The most common adverse reactions observed in clinical trials (frequency \geq 4% of patients) are inhibitor formation in previously untreated patients (PUPs) and minimally treated patients (MTPs), skin-related hypersensitivity reactions (e.g., rash, pruritus), infusion site reactions (e.g., inflammation, pain), and central venous access device (CVAD) line-associated infections in patients requiring a CVAD for intravenous administration.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

Previously Treated Patients (PTPs)

During the clinical studies conducted in PTPs, 451 adverse events (irrespective of the relationship to the study drug) were reported in the course of 24,936 infusions (1.8%). Twenty-four of the 451 adverse events were assessed as related to Helixate FS (0.1%). Adverse reactions reported by \geq 4% of the patients are listed in Table 3 below.

Table 3 Adverse Reactions (AR) in Previously Treated Patients (PTPs) with Frequency of \geq 4%

MedDRA Primary SOC	Preferred Term	Total No. of Patients: 73 No. of Patients with AR (%)	Total No. of Infusions: 24,936 AR per Infusion (%)
Skin and Subcutaneous Tissue Disorders	Rash, pruritus	6 (8.2%)	0.02
General Disorders and Administration Site Conditions	Infusion site reactions	3 (4.1%)	0.01

SOC = System Organ Class

Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs)

In clinical studies with pediatric PUPs and MTPs, 726 adverse events were reported in the course of 9,389 infusions (7.7%). Twenty-nine of the 726 adverse events were assessed as related to Helixate FS (0.3%).

Adverse reactions reported by \geq 4% of the patients are listed in Table 4 below.

Table 4 Adverse Reactions (AR) in Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs) with Frequency of \geq 4% (Age Range 2-27 months)

MedDRA Primary SOC	Preferred Term	Total No. of patients: 61 No. of Patients with AR (%)	Total No. of Infusions: 9,389 AR per Infusion (%)
Skin and Subcutaneous Tissue Disorders	Rash, pruritus, urticaria	10 (16.4)	0.01
Blood and Lymphatic System Disorders	Factor VIII inhibition	9 (15)*	N/A
General Disorders and Administration Site Conditions	Infusion site reactions	4 (6.6)	0.04

SOC = System Organ Class

*Denominator for *de-novo* inhibitors is N=60, since one patient had a pre-existing inhibitor.

Minimally Treated Patients (MTPs) in the Joint Outcome Study

In the Joint Outcome Study in MTP pediatric patients treated with routine prophylaxis or episodic enhanced treatment for 5.5 years, 46 of the 65 randomized patients experienced

adverse events over the study duration. Adverse events were not assessed for their relationship with Helixate FS.

Table 5 Adverse Events (AE) in MTPs in the Joint Outcome Study (Age Range 0-6 years)

MedDRA Primary SOC	Preferred Term	Total No. of Prophylaxis Arm Patients: 32 No. of Patients with AE (%)	Total No. of Enhanced Episodic Arm Patients: 33 No. of Patients with AE (%)
Surgical and Medical Procedures	Central venous catheterization, Catheter removal	19 (59)	18* (55)
Infections and Infestations	Central line infection	6 (19)	6 (18)
General Disorders and Administration Site Conditions	Pyrexia	1 (3)	4 (12)

SOC = System Organ Class

* Three patients from the enhanced episodic arm had catheter removal.

Immunogenicity

In clinical studies with 73 PTPs (defined as having more than 100 exposure days), one patient had a pre-existing inhibitor. In the other 72 patients, followed over 4 years, no *de-novo* inhibitors were observed.

In clinical studies with pediatric PUPs and MTPs, inhibitor development was observed in 9 out of 60 patients (15%), 6 were high titer¹($>$ 5 BU) and 3 were low-titer inhibitors. Inhibitors were detected at a median number of 7 exposure days (range 2 to 16 exposure days).

In the Joint Outcome Study with Helixate FS,⁵ *de-novo* inhibitor development was observed in 8 of 64 patients with negative baseline values (12.5%), 2 patients developed high titer¹ ($>$ 5 BU) and were withdrawn from the study. Six patients developed low-titer inhibitors. Inhibitors were detected at a median number of 44 exposure days (range 5 to 151 exposure days).

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post approval use of Helixate FS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Among patients treated with Helixate FS, cases of serious allergic/hypersensitivity reactions (which may include facial swelling, flushing, hives, blood pressure decrease, nausea, rash, restlessness, shortness of breath, tachycardia, tightness of the chest, tingling, urticaria, vomiting) have been reported, particularly in very young patients or patients who have previously reacted to other factor VIII concentrates.

The following table represents the post-marketing adverse reactions as MedDRA Preferred Terms.

Table 6 Post-Marketing Experience

MedDRA Primary SOC	Preferred Term
Blood and Lymphatic System Disorders	FVIII inhibition
Skin and Subcutaneous Tissue Disorders	Pruritus, urticaria, rash
General Disorders and Administration Site Conditions	Infusion site reaction
	Pyrexia
Immune System Disorders	Anaphylactic reaction, other hypersensitivity reactions

SOC = System Organ Class

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Helixate FS. It is also not known whether Helixate FS can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Helixate FS should be used during pregnancy only if clinically needed.

8.2 Labor and Delivery

There is no information available on the effect of factor VIII replacement therapy on labor and delivery. Helixate FS should be used only if clinically needed.

8.3 Nursing Mother

It is not known whether this drug is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if Helixate FS is administered

to nursing mothers. Helixate FS should be given to nursing mothers only if clinically needed.

8.4 Pediatric Use

Safety and efficacy studies have been performed in previously untreated and minimally treated pediatric patients. Children in comparison to adults present higher factor VIII clearance values and thus lower recovery of factor VIII. This may be explained by differences in body composition⁷ and should be taken into account when dosing or following factor VIII levels in such a population (see *Pharmacokinetics [12.3]*). Routine prophylactic treatment in children ages 0-2.5 years with no pre-existing joint damage has been shown to reduce spontaneous joint bleeding and the risk of joint damage. This data can be extrapolated to ages >2.5-16 years for children who have no existing joint damage (see *Clinical Studies [14]*).

8.5 Geriatric Use

Clinical studies with Helixate FS did not include patients aged 65 and over. Dose selection for an elderly patient should be individualized.

11 DESCRIPTION

Helixate FS Antihemophilic Factor (Recombinant) is a coagulation factor VIII produced by recombinant DNA technology. It is produced by Baby Hamster Kidney (BHK) cells into which the human factor VIII gene has been introduced.⁸ The cell culture medium contains Human Plasma Protein Solution (HPPS) and recombinant insulin, but does not contain any proteins derived from animal sources. Helixate FS is a purified glycoprotein consisting of multiple peptides including an 80 kD and various extensions of the 90 kD subunit. It has the same biological activity as factor VIII derived from human plasma. No human or animal proteins, such as albumin, are added during the purification and formulation processes of Helixate FS.

The purification process includes a solvent/detergent virus inactivation step in addition to the use of the purification methods of ion exchange chromatography, monoclonal antibody immunoaffinity chromatography, along with other chromatographic steps designed to purify recombinant factor VIII and remove contaminating substances.

Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.⁹⁻²¹ Several of the individual production and raw material preparation steps in the Helixate FS manufacturing process have been shown to decrease TSE infectivity of that experimental model agent. TSE reduction steps include the Fraction II+III separation step for HPPS (6.0 log₁₀) and an anion exchange chromatography step (3.6 log₁₀).

Helixate FS is formulated with the following as stabilizers (see *Table 7*) in the final container and is then lyophilized. The final product is a sterile, nonpyrogenic, preservative-free, powder preparation for intravenous (IV) injection. Intravenous administration of sucrose contained in Helixate FS will not affect blood glucose levels.

Table 7 Stabilizers Contained in Helixate FS Final Container

Stabilizer	250 IU, 500 IU, 1000 IU	2000 IU, 3000 IU
Sucrose	0.9 – 1.3%	0.9 – 1.2%
Glycine	21 – 25 mg/mL	20 – 24 mg/mL
Histidine	18 – 23 mmol/L	17 – 22 mmol/L

The following inactive ingredients/excipients are also contained in the final product:

Table 8 Inactive Ingredients/Excipients

Inactive Ingredient/Excipient	250 IU, 500 IU, 1000 IU	2000 IU, 3000 IU
Sodium	27 – 36 mEq/L	26 – 34 mEq/L
Calcium	2.0 – 3.0 mmol/L	1.9 – 2.9 mmol/L
Chloride	32 – 40 mEq/L	31 – 38 mEq/L
Polysorbate 80	64 – 96 µg/mL	64 – 96 µg/mL
Sucrose	28 mg/vial	52 mg/vial
Imidazole, tri-n-butyl phosphate, and copper	Trace amounts	Trace amounts

Each vial of Helixate FS contains the labeled amount of recombinant factor VIII in international units (IU). One IU, as defined by the World Health Organization standard for blood coagulation factor VIII, human, is approximately equal to the level of factor VIII activity found in 1 mL of fresh pooled human plasma.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Helixate FS temporarily replaces the missing clotting factor VIII that is needed for effective hemostasis.

12.2 Pharmacodynamics

The aPTT is prolonged in patients with hemophilia. Determination of activated partial thromboplastin time (aPTT) is a conventional in vitro assay for biological activity of factor VIII. Treatment with Helixate FS normalizes the aPTT over the effective dosing period.

12.3 Pharmacokinetics

The pharmacokinetic properties of Helixate FS were investigated in two separate studies in previously treated patients, adults and children.

Pharmacokinetic studies with Helixate FS were conducted in 20 PTPs (ages 12 to 33 years) with severe hemophilia A in North America. The pharmacokinetic parameters for Helixate FS were measured in a randomized, crossover clinical trial with the predecessor HELIXATE product with a single dose administration of 50 IU/kg. After 24 weeks, the same dose of Helixate FS was administered to the same patients. The recovery and half-life data for Helixate FS were unchanged after 24 weeks of continued treatment with sustained efficacy and no evidence of factor VIII inhibition (see *Table 9*).

Table 9 Pharmacokinetic Parameters for Helixate FS Compared to HELIXATE

Parameter	Helixate FS		HELIXATE
	Initial PK Mean (±SD)	PK at week 24 Mean (±SD)	Reference Mean (±SD)
AUC (IU • h/dL)	1588.05 ± 344.32	1487.08 ± 381.73	1879.02 ± 412.32
C _{max} (IU/dL)	114.95 ± 20.19	109.42 ± 20.09	127.40 ± 33.21
Half-life (hr)	13.74 ± 1.82	14.60 ± 4.38	14.07 ± 2.62
In Vivo Recovery (IU/dL / IU/kg)	2.20 ± 0.34	2.11 ± 0.37	2.43 ± 0.60

The pharmacokinetics of Helixate FS were investigated in pediatric PTPs (4.4-18.1 years of age, average age 12).⁷ The pharmacokinetic parameters in children compared to adults show differences in higher clearance, lower incremental in vivo factor VIII recovery and a shorter factor VIII half-life. This might be explained by differences in body composition such as body surface area and plasma volume. The pharmacokinetic parameters are depicted in *Table 10*.

Table 10 Pharmacokinetic Parameters for Helixate FS in Children

Parameter	Mean (range)
AUC (IU • h/dL)	1320.0
Clearance (mL/h•kg)	4.1
Half-life (hr)	10.7 (7.8 – 15.3)
In Vivo Recovery (IU/dL / IU/kg)	1.9 (1.25 – 2.76)

13 NONCLINICAL TOXICOLOGY

Preclinical studies evaluating Helixate FS in hemophilia A with mice, rats, rabbits, and dogs demonstrated safe and effective restoration of hemostasis. Doses several fold higher than the recommended clinical dose (related to body weight) did not demonstrate any acute or subacute toxic effect for Helixate FS in laboratory animals.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted with Helixate FS to assess its mutagenic or carcinogenic potential and impairment of fertility. Helixate FS has been shown to be comparable to the predecessor product with respect to its biochemical and physicochemical properties, as well as its non-clinical in vivo pharmacology and toxicology. By inference, the predecessor product and Helixate FS would be expected to have equivalent mutagenic and carcinogenic potential.

The predecessor product did not demonstrate reverse mutation or chromosomal aberrations at doses substantially greater than the maximum expected clinical dose. In vivo evaluation with the predecessor product in animals using doses ranging between 10 and 40 times the expected clinical maximum also indicated that the predecessor product did not possess a mutagenic potential. Long-term investigations of carcinogenic potential in animals have not been performed due to the immune response to heterologous proteins in all non-human mammalian species.

14 CLINICAL STUDIES

14.1 Previously Treated Patients (PTPs)

A total of 73 patients with severe (≤ 2% FVIII) hemophilia A, ages 12–59, who had been previously treated with other recombinant or with plasma-derived AHF products, were treated up to 54-months in open label studies with Helixate FS in Europe and North America. A total of 5,684 bleeding episodes were treated during the studies.

Patients could be treated on demand or on prophylaxis. Regularly scheduled prophylaxis treatment represented 76% of all infusions (treatment regimens of 2-3 infusions per week) (see Table 11).

Table 11 Previously Treated Patients (PTPs) Clinical Trial Results

Clinical Parameters	Results
No. of Infusions of Helixate FS Administered	24,924
No. of IU Administered	45 million IU
No. of Bleeds Treated with Helixate FS	5,684
Percentage of Bleeds Treated with One or Two Infusions of Helixate FS	one infusion: 79.7% two infusions: 13.0% total: 92.7%
Mean Helixate FS Dose per Treatment Infusion (in Europe and North America, Respectively)	Approximately 32.5 and 29.6 IU/kg per treatment infusion

A total of 31 patients received Helixate FS for 43 surgical procedures during the PTP studies. There were both minor and major surgery types, 27 and 16 respectively. The surgeon or treating physician assigned a rating to the hemostatic outcome according to 4 categories; "excellent", "good", "moderate", or "none". Hemostasis was rated as satisfactory ("excellent" or "good") in all cases (see Table 13).

14.2 Previously Untreated and Minimally Treated Patients (PUPs and MTPs)

Helixate FS has been used in the treatment of bleeding episodes in previously untreated pediatric patients (PUPs) and minimally treated patients (MTPs) with severe (< 2% FVIII) hemophilia A. There were 37 PUPs and 24 MTPs (defined as having equal to or less than 4 exposure days) treated with a total of 9,419 infusions of Helixate FS for a follow up duration up to 3.1 years. A total of 1047 bleeding episodes were treated.

Table 12 Previously Untreated and Minimally Treated Patients (PUPs and MTPs) Clinical Trial Results

Clinical Parameters	Results
No. of Infusions of Helixate FS Administered	9,419
No. of Exposure Days to Helixate FS (median)	115 exposure days
No. of IU Administered	7.5 million IU
No. of Bleeds Treated with Helixate FS	1,047
Percentage of Bleeds Treated with One or Two Infusions of Helixate FS	one infusion: 73.1% two infusions: 15.0% total: 88.1%

A total of 29 surgical procedures were performed in 23 patients during the PUPs and MTPs study. There were both minor and major surgery types, 23 and 6 respectively. The surgeon or treating physician assigned a rating to the hemostatic outcome according to 4 categories; "excellent", "good", "moderate", or "none". Hemostasis was rated as satisfactory ("excellent" or "good") in all cases (see Table 13).

Table 13 Surgical Procedures Performed During PTPs and PUPs/MTPs Clinical Trials

Type of Surgery	PTPs (N=31)		PUPs/MTPs (N=23)	
	No. of Surgical Events	Outcome "Good" or "Excellent"	No. of Surgical Events	Outcome "Good" or "Excellent"
Minor Surgery (i.e. tooth extractions, catheter implantations, liver biopsies)	27	100%	23	100%
Major Surgery (i.e. joint replacements, craniotomies, gastrointestinal resection)	16	100%	6	100%
Total	43		29	

14.3 Pediatric Prophylaxis and Joint Damage Risk Reduction

A total of 65 boys less than 30 months of age with severe hemophilia A (FVIII level ≤ 2 IU/dL) and with ≤ 2 bleeds into each index joint and normal baseline joint imaging, were observed for up to 5.5 years in a multicenter, open-label, prospective, randomized,

controlled clinical study.⁵ Patients received either 25 IU/kg every other day (primary prophylaxis; n=32) or at least 3 doses totaling a minimum of 80 IU/kg at the time of a bleeding episode (enhanced episodic; n=33). Joint damage was evaluated by magnetic resonance imaging (MRI) or radiography, as well as the frequency of bleeding episodes. Joint damage detected by MRI or radiography in the ankles, knees, and elbows (i.e. index joints) was statistically significantly lower (p=0.002) for subjects receiving prophylactic therapy (7%) than for subjects receiving episodic therapy (42%). This corresponds to a 6.29-fold relative risk of joint damage for subjects treated with enhanced episodic therapy compared to prophylaxis. The mean rate of index joint hemorrhages for subjects on episodic therapy was 4.89 bleeds per year, versus 0.63 bleeds per year observed in the prophylaxis arm. Three of 33 (9.1%) subjects in the episodic arm experienced recurrent life threatening bleeds (intracranial, gastrointestinal) compared to no subjects in the prophylaxis arm. On a per joint basis, joints in the regular prophylaxis arm were 8-fold more likely to remain damage-free than those in the episodic arm. Joint damage was most frequently observed in ankle joints and was detected at higher rates by MRI than by radiography. Ankles were also the index joint that demonstrated the highest frequency of bleeding events in this study (left ankle, mean 2.7 hemorrhages; right ankle, mean 2.6 hemorrhages).

As shown in Table 14 below, the incidence of joint damage was statistically significantly lower in the prophylactic group as compared to the episodic treatment group when assessed by MRI, or either MRI or radiography, using predefined criteria (described below) for establishing joint damage. However, there was no statistically significant difference between the two groups when joint damage was assessed by radiography alone.

To evaluate joint damage, MRIs were scored using a scale developed by Nuss et al.²², and X-rays were scored using the method of Pettersson et al.²³ Both scales have been validated in various clinical trials and are routinely used for joint damage evaluation in hemophiliacs. Joint damage was defined as bone and/or cartilage damage including subchondral cysts, erosions and cartilage loss with narrowing of joint space. This corresponded to a total MRI score of ≥ 7 or an X-ray score of ≥ 1 in any of the following categories: subchondral cysts, erosions of joint surfaces or narrowing of joint spaces. Images were read separately by two independent radiologists centrally. Any discrepant reading was read by an independent third radiologist who was not aware of the initial reading results. The concordant reading of two out of three readers was used for analysis purposes.

Table 14 Subjects with Joint Damage (Subjects with Available Baseline and Endpoint Data)

Endpoint Assessment	Prophylaxis		Episodic Therapy		p-value
	Incidence (%)	Relative Risk (95% CI)	Incidence (%)	Relative Risk (95% CI)	
MRI	2/27 (7%)	0.17 (0.04, 0.67)	13/29 (45%)	6.05 (1.50, 24.38)	0.002
Radiography	1/28 (4%)	0.19 (0.02, 1.55)	5/27 (19%)	5.19 (0.65, 41.54)	0.101
MRI or Radiography	2/30 (7%)	0.16 (0.04, 0.65)	13/31 (42%)	6.29 (1.55, 25.55)	0.002

Relative Risk is the risk of damage to one or more index joints on the given therapy as compared to the other therapy.

P-value is from the 2-sided Fisher Exact Test comparing the incidence of joint damage between treatment groups.

As shown in Table 15 below, the assessment of endpoints in all randomized subjects assuming that those without complete baseline and endpoint data are treatment failures (intention-to-treat analysis). The incidence of joint damage was statistically significantly lower in the prophylactic group as compared to the episodic treatment group, with similar p-values, when assessed by MRI, or either MRI or radiography.

Table 15 Subjects with Joint Damage (All Randomized Subjects Assuming Subjects without Complete Baseline and Endpoint Data as Treatment Failures)

Endpoint Assessment	Prophylaxis (n=32)		Episodic Therapy (n=33)		p-value
	Incidence (%)	Relative Risk (95% CI)	Incidence (%)	Relative Risk (95% CI)	
MRI	7 (22%)	0.42 (0.20, 0.88)	17 (52%)	2.35 (1.13, 4.90)	0.020
Radiography	5 (16%)	0.47 (0.18, 1.20)	11 (33%)	2.13 (0.83, 5.45)	0.150
MRI or Radiography	8 (25%)	0.43 (0.22, 0.85)	19 (58%)	2.30 (1.18, 4.49)	0.012

Relative Risk is the risk of damage to one or more index joints on the given therapy as compared to the other therapy.

P-value is from the 2-sided Fisher Exact Test comparing the incidence of joint damage between treatment groups.

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Helixate FS is available as a kit in the following single-use glass vial sizes. A suitable volume of Sterile Water for Injection, USP and Mix2Vial™ filter transfer device (see *Preparation and Reconstitution [2.5]*) are provided in the kit.

NDC Number	Approximate FVIII Activity (IU)	Diluent (mL)
0053-8131-02	250	2.5
0053-8132-02	500	2.5
0053-8133-02	1000	2.5
0053-8134-02	2000	5.0
0053-8135-02	3000	5.0

Actual factor VIII activity in IU is stated on the label of each Helixate FS vial.

16.2 Storage and Handling

Product as Packaged for Sale:

- Store Helixate FS under refrigeration (2–8°C or 36–46°F).
- Storage of lyophilized powder at room temperature (up to 25°C or 77°F) for 3 months, such as in home treatment situations, may be done. If Helixate FS is stored outside the refrigerator, please add the date removed from refrigeration and note a new expiry date on the carton and vial. The new expiry date should be 3 months from the date product is removed from the refrigerator, or the previously stamped expiry date, whichever is shorter.
- Do not return to the refrigerator once Helixate FS is removed from refrigeration.
- Do not use Helixate FS after the expiration date indicated on the vial.
- Do not freeze.
- Protect from extreme exposure to light and store the lyophilized powder in the carton prior to use.

Product After Reconstitution:

- Administer Helixate FS within 3 hours after reconstitution.
- It is recommended to use the administration set provided.

17 PATIENT COUNSELING INFORMATION

See Patient Product Information (PPI) and Instructions for Use.

Advise patients to report any adverse reactions or problems following Helixate FS administration to their physician or healthcare provider.

- Allergic-type hypersensitivity reactions have been reported with Helixate FS. Warn patients of the early signs of hypersensitivity reactions [including hives (rash with itching), generalized urticaria, tightness of the chest, wheezing, hypotension] and anaphylaxis. Advise patients to discontinue use of the product if these symptoms occur and seek immediate emergency treatment with resuscitative measures such as the administration of epinephrine and oxygen.
- In clinical studies with Helixate FS, a 15% incidence of inhibitor development was observed in PUPs/MTPs and zero de-novo inhibitors were observed with the PTPs. Inhibitor formation may occur at any time in the treatment of a patient with hemophilia A. Advise patients to contact their physician or treatment center for further treatment and/or assessment, if they experience a lack of clinical response to factor VIII replacement therapy, as this may be a manifestation of an inhibitor.
- Advise patients to consult with their healthcare provider prior to travel. While traveling advise patients to bring an adequate supply of Helixate FS based on their current regimen of treatment.

17.1 FDA-Approved Patient Labeling – Patient Product Information (PPI) Helixate FS (he-likes-ät) Antihemophilic Factor (Recombinant) Formulated with Sucrose

This leaflet summarizes important information about Helixate FS. Please read it carefully before using this medicine. This information does not take the place of talking with your healthcare provider, and it does not include all of the important information about Helixate FS. If you have any questions after reading this, ask your healthcare provider.

Do not attempt to self-infuse unless you have been taught how by your healthcare provider or hemophilia center.

What is Helixate FS?

Helixate FS is a medicine used to replace clotting factor (factor VIII or antihemophilic factor) that is missing in people with hemophilia A (also called “classic” hemophilia). Hemophilia A is an inherited bleeding disorder that prevents blood from clotting normally.

Helixate FS is used to prevent and control bleeding in adults and children (0-16 years) with hemophilia A. Your healthcare provider may give you Helixate FS when you have surgery. Helixate FS can reduce the number of bleeding episodes when used regularly and reduce the risk of joint damage in children.

Helixate FS is not used to treat von Willebrand’s Disease.

Who should not use Helixate FS?

You should not use Helixate FS if you

- are allergic to rodents (like mice and hamsters).
- are allergic to any ingredients in Helixate FS.

Tell your healthcare provider if you are pregnant or breast-feeding because Helixate FS may not be right for you.

What should I tell my healthcare provider before I use Helixate FS?

Tell your healthcare provider about all of your medical conditions.

Tell your healthcare provider and pharmacist about all of the medicines you take, including all prescription and nonprescription medicines, such as over-the-counter medicines, supplements, or herbal remedies.

Tell your healthcare provider if you have been told that you have inhibitors to factor VIII (because Helixate FS may not work for you).

What are the possible side effects of Helixate FS?

You could have an allergic reaction to Helixate FS. Call your healthcare provider right away and stop treatment if you get

- rash or hives
- itching
- tightness of the chest or throat

- difficulty breathing
- light-headed, dizziness
- nausea
- decrease in blood pressure

Your body can also make antibodies, called “inhibitors”, against Helixate FS, which may stop Helixate FS from working properly. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to factor VIII.

Other common side effects of Helixate FS are

- Local injection site reactions (pain, swelling, irritation at infusion site)
- Infections from implanted injection device

Tell your healthcare provider about any side effect that bothers you or does not go away. Finding veins for injections may be difficult in young children. When frequent injections are required your child’s healthcare provider may propose to have a device surgically placed under the skin to facilitate access to the bloodstream. These devices may result in infections.

These are not all the possible side effects with Helixate FS.

You can ask your healthcare provider for information that is written for healthcare professionals.

How do I store Helixate FS?

Do not freeze Helixate FS.

Helixate FS vials containing powdered product (without sterile diluent added) should be stored in a refrigerator (2°C–8°C [36°F–46°F]), or at room temperature (up to 25°C or 77°F) for up to 3 months.

If you choose to store Helixate FS at room temperature, be sure to note on the carton the date that the product is removed from refrigeration. Store vials in their original carton and protect them from extreme exposure to light.

Reconstituted product (after mixing dry products with wet diluent) must be used within 3 hours and cannot be stored.

Throw away any unused Helixate FS after the expiration date.

Do not use reconstituted Helixate FS if it is not clear to slightly cloudy and colorless.

What else should I know about Helixate FS and hemophilia A?

Medicines are sometimes prescribed for purposes other than those listed here. Do not use Helixate FS for a condition for which it is not prescribed. Do not share Helixate FS with other people, even if they have the same symptoms that you have.

This leaflet summarizes the most important information about Helixate FS. If you would like more information, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about Helixate FS that was written for healthcare professionals.

Instructions for use

How should I take Helixate FS?

Do not attempt to self-infuse unless you have been taught how by your healthcare provider or hemophilia center.

See the step-by-step instructions for reconstituting Helixate FS at the end of this leaflet and the Mix2Vial™ filter transfer device instruction leaflet provided.

You should always follow the specific instructions given by your healthcare provider. The steps listed below are general guidelines for using Helixate FS. If you are unsure of the procedures, please call your healthcare provider before using.

Call your healthcare provider right away if bleeding is not controlled after using Helixate FS.

Your healthcare provider will prescribe the dose that you should take.



Your healthcare provider may need to take blood tests from time to time.


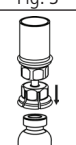
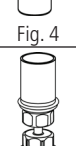
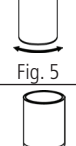

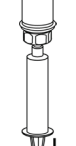
Talk to your healthcare provider before traveling. You should plan to bring enough Helixate FS for your treatment during this time.

Carefully handle Helixate FS. Dispose of all materials, including any leftover reconstituted Helixate FS product, in an appropriate container.

Reconstitution and use of Helixate FS

Always work on a clean flat surface and wash your hands before performing the following procedures:

1.	Warm the unopened diluent and the concentrate to a temperature not to exceed 37°C or 99°F.	
2.	Place the product vial, diluent vial and Mix2Vial™ on a flat surface.	
3.	Ensure product and diluent vial flip caps are removed and the stoppers are treated with an aseptic solution and allowed to dry prior to opening the Mix2Vial package.	
4.	Open the Mix2Vial package by peeling away the lid (Fig. 1). Leave the Mix2Vial in the clear package. Place the diluent vial on an even surface and hold the vial tight. Grip the Mix2Vial together with the package and snap the blue end onto the diluent stopper (Fig. 2).	 <p>Fig. 1</p>  <p>Fig. 2</p>

5.	Carefully remove the clear package from the Mix2Vial set. Make sure that you only pull up the package and not the Mix2Vial set (Fig. 3).	 <p>Fig. 3</p>
6.	With the product vial firmly on a surface, invert the diluent vial with the set attached and snap the transparent adapter onto the product vial stopper (Fig. 4). The diluent will automatically transfer into the product vial.	 <p>Fig. 4</p>
7.	With the diluent and product vial still attached, gently swirl the product vial to ensure the powder is fully dissolved (Fig. 5). Do not shake vial.	 <p>Fig. 5</p>
8.	With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the blue diluent-side of the Mix2Vial set and unscrew the set into two pieces (Fig. 6).	 <p>Fig. 6</p>
9.	Draw air into an empty, sterile syringe. While the product vial is upright, screw the syringe to the Mix2Vial set. Inject air into the product vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly (Fig. 7).	 <p>Fig. 7</p>
10.	Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the syringe plunger facing down) and unscrew the syringe from the Mix2Vial set (Fig. 8). Attach the syringe to an administration set made with microbore tubing. Use of other administration sets without microbore tubing may result in a larger retention of the solution within the administration set.	 <p>Fig. 8</p>
11.	If the same patient is to receive more than one bottle, the contents of two bottles may be drawn into the same syringe through a separate unused Mix2Vial set before attaching the vein needle.	
12.	Helixate FS should be inspected visually for particulate matter and discoloration prior to administration.	

Rate of administration

The entire dose of Helixate FS can usually be infused within 1 to 15 minutes. However, your healthcare provider will determine the rate of administration that is best for you.

Resources at CSL Behring available to the patient:

For Adverse Reaction Reporting contact:

CSL Behring Pharmacovigilance Department at 1-866-915-6958

Contact CSL Behring to receive more product information:

Consumer Affairs 1-888-508-6978

Customer Support 1-800-683-1288

Reimbursement Services 1-800-676-4266

For more information, visit www.HelixateFS.com

Manufactured by:

Bayer HealthCare LLC Tarrytown, NY 10591 USA

U.S. License No. 8 (License Holder: Bayer Corporation)

Distributed by:

CSL Behring LLC Kankakee, IL 60901 USA

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