Helixate® FS
Antihemophilic Factor (Recombinant)
Formulated with Sucrose

ZLB Behring

DESCRIPTION

Helixate® FS is a sterile, purified, recombinant factor VIII concentrate that has been manufactured using recombinant DNA technology. Helixate® FS is intended for use in the treatment of classical hemophilia (hemophilia A), and is produced by a recombinant process. The final product is a highly purified glycoprotein containing multiple amino acids, including 80% and various extensions of the 80-kDa subunit. It has the same biological activity as FVIII derived from human plasma. Compared to its predecessor product HELIXATE®, Helixate® FS is a purified and recombinant FVIII and contains proteins derived from animal sources. Helixate® FS is highly purified and contains minimal amounts of contaminants such as copper and calcium. In addition, the helixate® FS manufacturing process does not include the Fraction II+III separation step for Human Plasma Protein Solution (6.0 log10) and an anion exchange chromatography step (3.6 log10). These studies provide reasonable assurance that low levels of copper (nCGD) agent infectivity, if present in the starting material, would be removed.

None.

WARNINGS

Known intolerance or allergic reactions to constituents of the preparation.

Administration

None.

INDICATIONS AND USAGE

Helixate® FS is indicated for the treatment of classical hemophilia (hemophilia A) in which there is a demonstrated deficiency of activity of the plasma clotting factor FVIII. Helixate® FS provides a means of temporarily replacing the missing clotting factor in order to correct or prevent bleeding episodes, or in order to perform an elective surgery in hemophiliacs.

Clinical studies in previously untreated patients (PUPs) and minimally treated (MTP) patients. In ongoing studies, 61 PUPs/MTPs have been treated with Helixate® FS. Hemorrhage was satisfactory in all cases.

In clinical studies with Helixate® FS in previously treated patients, 159 adverse events were reported in the course of 4160 infusions (2.6%). Only 13 events were reported by the investigator as at least remotely drug-related. Another 7 events were nonassessable. Thus 20 events in 11 patients were considered to be either nonassessable or at least remotely related to Helixate® FS administration, for an incidence of 0.5% relative to the number of infusions administered. Events that were at least remotely drug-related included: local injection site reactions (2), dizziness (2), rash (2), unusual taste in the mouth (1), mild increase in blood pressure (1), pruritus (1), desensitization (1), nausea (1), and thirst (1). No FVIII inhibitors have developed in the 72 PUPs with severe hemophilia A who have received Helixate® FS for a mean of 54 exposure days. In clinical studies with previously untreated patients (PUPs) and minimally treated (MTP) pediatric patients, 18 adverse events were reported by the clinical investigators as at least possibly related to the study drug including anaphylaxis and urticaria.

ADVERSE REACTIONS

Calcium phosphate (NMT 0.6 µg/1000 IU), tris(hydroxymethyl)aminomethane (NMT 5 µg/1000 IU), and sucrose (NMT 0.6 µg/1000 IU). The product contains no preservatives. The amount of sucrose in each vial is 28 mg. Intravenous administration of sucrose contained in Helixate® FS will not affect blood glucose levels. Each unit of Helixate® FS contains the labeled amount of recombinant FVIII in international units (IU). One IU, as defined by the World Health Organization standard for blood coagulation FVIII, is human, is equal to the level of FVIII activity found in 1 mL of fresh pooled human plasma. Helixate® FS must be administered by the intravenous route.

CLINICAL PHARMACOLOGY

Pharmacokinetic studies were conducted in 20 patients with severe hemophilia A in North America. In this comparative pharmacokinetic study, Helixate® FS was shown to be similar to its predecessor product HELIXATE. Mean FVIII recovery measured 10 minutes following infusion was 2.1 ± 0.3 %/IU/kg for Helixate® FS and 2.4 ± 0.7 %/IU/kg for HELIXATE. The two recoveries were not statistically different (confidence interval 0.815–1.01). The mean peak concentration for recombinant FVIII (FS) infusion in stable futility was a mean of approximately 13 hours, which has previously been shown to be similar to plasma-derived Antithemophilic Factor (AHF). The actual partial thromboplastin time shortened appropriately both with FVIII and FVIII-FS. The recovery and half-life data for FVIII-FS were unchanged after 24 weeks of exclusive treatment indicating continued efficacy and no evidence of FVIII inhibition. The mean FVIII recovery measured 10 minutes following a dose of FVIII (24 patients) after 2 weeks of treatment with FVIII-FS was 2.71%/IU/kg, which was unchanged from FVIII recovery determined at baseline and at weeks 4 and 12.

Seventy-one patients with severe hemophilia A, ages 12–59, who had been previously treated with other recombinant and plasma-derived AHF products, were enrolled in 6-month studies of home therapy with FVIII-FS in Europe and North America. A total of 3995 infusions have been administered under this portion of the study, or 7.4 million units of FVIII-FS. Treatment of 659 bleeding episodes during the study period required 951 infusions of rFVIII-FS. The majority of bleeding episodes (89.5%) were treated successfully with one or two infusions, using a mean dosage of approximately 28 IU/kg per treatment infusion. Regularly scheduled treatment accounts for a mean of 71% of all treated episodes. Ten patients have had inhibitor development in 37 patients (after 24 weeks of treatment with FVIII-FS) was 2.1%/IU/kg, which was unchanged from FVIII recovery determined at baseline and at weeks 4 and 12.

Monitoring

None.

DOSAGE AND ADMINISTRATION

Each bottle of Helixate® FS has the FVIII potency in international units stated on the label based on the one-stage assay methodology. The reconstituted product must be administered within 3 hours after reconstitution.

GENERAL APPROACH TO TREATMENT AND ASSESSMENT OF TREATMENT EFFICACY

The dosages described below are presented as general guidance. Use of other dosages for patients generally not possible. Administration of Helixate® FS for treatment of severe hemophilia A should be individualized according to the severity of the bleeding disorder, the severity of the hemophilia, the presence of inhibitors, and the FVIII level desired. It is often critical to follow the course of therapy with FVIII level assays. The clinical effect of FVIII is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more FVIII than estimated to achieve a satisfactory clinical response. The presence of an inhibitor is not a reason for failure to attain the expected FVIII levels. If bleeding is not controlled after administration of the calculated dosage, the presence of a circulating inhibitor in the patient should be suspected. Its presence should be substantiated and the inhibitor level quantitated by an appropriate assay. When an inhibitor is present, the dose of recombinant FVIII should be increased extremely variable among different patients, and the optimal treatment can be determined only by the clinical response. Some patients with low-titer inhibitors (<10 BU) can be successfully treated with FVIII preparations without a resultant anemogenic rise in inhibitor titers to FVIII levels and clinical response to treatment does not appear to be adequate. Use of alternative treatment products, such as Factor IX Complex concentrates, Antithemophilic Factor (Porcine), recombinant Factor VIII or Anti-Inhibitor Coagulant Complexes, may be necessary for patients with anamnestic responses to FVIII treatment and/or high-titer inhibitors.

Calculation of Dosage

The in vivo potency of FVIII in clinical studies was shown to be equivalent to that of Helixate® FS per kilogram of body weight (IU/kg) by 2% per IU per kg. This method of calculation is based on clinical findings with the use of other plasma-derived and recombinant AHF products and is illustrated in the following examples:

(see next page)
The dosage necessary to achieve hemostasis depends upon the type and severity of the bleeding episode, according to the following general guidelines:

**Hemorrhagic event** | Therapeutically necessary plasma level of FVIII activity | Dosage necessary to maintain the therapeutic plasma level
--- | --- | ---
Minor hemorrhage | 20–40% | 10–20 IU per kg per bleeding event.

Moderate to major hemorrhage | 30–60% | 15–30 IU per kg per bleeding event.

Surgery | Major surgical procedures | ~100% Preparatory dose 50 IU/kg Verify ~100% activity prior to surgery. Repeat as necessary after 6 to 12 hours initially and every 8–12 hours until healing is complete.

Fractures | Head trauma | Minor surgical procedures

**Prophylaxis**

Self-injections may also be administered on a regular schedule for prophylaxis of bleeding, as reported by Nilsson et al.

**Instructions for Use**

Reconstitution and product administration must be done with caution. Perforate 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 Antihemophilic Factor (Recombinant) product, in accordance with biohazard procedures.

Reconstitution

Always wash your hands before performing the following procedures:

1. **Vacuum Transfer**
   1. Warm the unopened diluent and the concentrate to a temperature not exceeding 37°C, 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).
   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).
   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.
   7. With the diluent and product vial still attached, gently swirl the product vial to ensure the product is fully dissolved (Fig. 5). Do not shake vial.
   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).
   9. Draw air into an empty, sterile syringe. While the product vial is upright, screw the syringe to the Mix2Vial set. 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).
   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. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**Rate of Administration**

The rate of administration should be adapted to the response of the individual patient, but the administration may be prolonged to 5 to 10 minutes or less, if well tolerated.

**HOW SUPPLIED**

Helixate® FS Antihemophilic Factor (Recombinant) is supplied in the following single use bottles. A suitable volume of Sterile Water for Injection, USP and Mix2Vial™ filter transfer set are provided. The actual potency is printed on the label and the carton.

**NDC Number** | Approximate FVIII Activity (IU) | Dosage | Diluent (mL)
--- | --- | --- | ---
0053-8130-01 | 250 | L | 2.5
0053-8130-02 | 500 | M | 2.5
0053-8130-03 | 1000 | H | 2.5

**STORAGE**

Helixate FS should be stored in a refrigerator at 2–8°C (36–46°F) for stable storage or disposal, except for up to 3 months, such as in home treatment situations. Do not freeze. Do not use beyond the expiration date indicated on the bottle. Protect from extreme exposure to light and store the lyophilized powder in the carton prior to use.

**REFERENCES**


Product Website: www.hemophiliastore.com

18530-01 (Revised April, 2006)