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

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FULL PRESCRIBING INFORMATION

Helixate® FS

Antihemophilic Factor (Recombinant)

Formulated with Sucrose

1 INDICATIONS AND USAGE

Helixate® FS is a recombinant antihemophilic factor indicated for:

- On-demand treatment and control of bleeding episodes in adults and children with hemophilia A.
- Perioperative management of bleeding in adults and children with hemophilia A.
- Routine prophylaxis to reduce the frequency of bleeding episodes in children with hemophilia A and to reduce the risk of joint damage in children without pre-existing joint damage.
- Routine prophylaxis to reduce the frequency of bleeding episodes in adults with hemophilia A.

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

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

2.1 Dose

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.

Each vial of Helixate FS has the recombinant factor VIII (FVIII) potency in international units (IU, unit) stated on the label. One IU (unit), 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.

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

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

or

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

Titrate dose 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 appropriate laboratory tests, including serial factor VIII activity assays, are performed [see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

On-Demand Treatment and Control of Bleeding Episodes

A guide for dosing Helixate FS for on-demand treatment and control of bleeding episodes is provided in Table 1. The goal of treatment is to maintain a plasma factor VIII activity level at or above the plasma levels (in % of normal or in IU/dL) outlined in Table 1.

Table 1 Dosing for On-Demand Treatment and Control of Bleeding Episodes

<table>
<thead>
<tr>
<th>Type of Bleeding Episodes</th>
<th>Factor VIII Level Required (IU/dL or % normal)</th>
<th>Dose (IU/kg)</th>
<th>Frequency of Doses (hours)</th>
<th>Duration of Therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Early hemorrhosis, minor muscle or oral bleeds.</td>
<td>20 – 40</td>
<td>10 – 20</td>
<td>Repeat dose if there is evidence of further bleeding.</td>
<td>Until bleeding is resolved</td>
</tr>
<tr>
<td>Moderate Bleeding into muscles, bleeding into the oral cavity, definite hemarthroses, and known trauma.</td>
<td>30 – 60</td>
<td>15 – 30</td>
<td>12 – 24</td>
<td>Until bleeding is resolved</td>
</tr>
<tr>
<td>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.</td>
<td>80 – 100</td>
<td>Initial: 40 – 50 Repeat: 20 – 25</td>
<td>8 – 12</td>
<td>Until bleeding is resolved</td>
</tr>
</tbody>
</table>

For intravenous use after reconstitution only.

2.2 Preparation and Reconstitution

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

Reconstitute and administer Helixate FS with the components provided with each package. If any component of the package is opened or damaged, do not use this component. Product reconstitution, administration, and handling of the administration set and needles must be done with caution because percutaneous puncture with a needle contaminated with blood can transmit infectious viruses, including HIV (AIDS) and hepatitis. Place needles in a sharps container after single use. Discard all equipment, including any reconstituted Helixate FS product, in an appropriate container. Obtain immediate medical attention if injury occurs.

For any questions about the handling, reconstitution and administration of Helixate FS, contact CSL Behring Medical Affairs at 1-800-504-5434. For instructions, patients should follow the recommendations in the FDA-Approved Patient Labeling.

The procedures below are provided as general guidelines for the reconstitution of Helixate FS.

- Work on a clean flat surface and wash hands thoroughly using soap and warm water before performing the procedures.
- Reconstitute the product with the components provided with each package. If any component of the package is opened or damaged, do not use this component.
- Filter the reconstituted product prior to administration to remove potential particulate matter in the solution. Filtering can be achieved by using the Mix2Vial® vial adapter.

Vacuum Transfer and Reconstitution

1. Prepare the product under aseptic conditions.

2. Warm the unopened diluent and the concentrate to a temperature not to exceed 37°C or 99°F.

3. Place the product vial, diluent vial and Mix2Vial on a flat surface.

4. 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.
5. 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).

6. 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).

7. 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.

8. 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.

9. 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).

10. 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).

11. 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.

12. 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.

2.3 Administration
For intravenous use after reconstitution only.
- Inspect Helixate FS visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Turbid or discolored solution should be discarded.
- Store the reconstituted Helixate FS at room temperature prior to administration, but administer it within 3 hours.
- Administer Helixate FS over a period of 1 to 15 minutes. Adapt the rate of administration to the response of each individual patient. Determine the pulse rate before and during administration of Helixate FS. If there is a significant increase in pulse rate, reduce the rate of administration or temporarily halt the infusion allowing the symptoms to disappear promptly.

3 DOSAGE FORMS AND STRENGTHS
Helixate FS is available as a lyophilized powder in single use glass vials containing nominally 250, 500, 1000, 2000, and 3000 International Units (IU, unit).
Each vial of Helixate FS is labeled with the recombinant antihemophilic factor activity expressed in International Units 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 life-threatening hypersensitivity reactions, including anaphylaxis to mouse or hamster protein or other constituents of the product (sucrose, glycite, histidine, sodium, calcium chloride, polysorbate 80, imidazole, tri-n-butyl phosphate, copper).

5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
Hypersensitivity reactions, including anaphylaxis have been reported with Helixate FS. Reported symptoms included facial swelling, flushing, hives, decrease in blood pressure, nausea, rash, restlessness, shortness of breath, tachycardia, tightness of the chest, tingling, urticaria, and vomiting. Helixate FS contains trace amounts of mouse immunoglobulin G (MolgG) and hamster (BHK) proteins [see Description (11)]. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins. Discontinue Helixate FS if symptoms occur and seek immediate emergency treatment.

5.2 Neutralizing Antibodies
Neutralizing antibodies (inhibitors) have been reported following administration of Helixate FS predominantly in previously untreated patients (PUPs) [see Adverse Reactions (6)]. Carefully monitor patients for the development of factor VIII inhibitors, using appropriate clinical observations and laboratory tests. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, perform an assay that measures factor VIII inhibitor concentration [see Warnings and Precautions (5.4)].

5.3 Cardiovascular Risk Factors
Hemophilic patients with cardiovascular risk factors or diseases may be at the same risk to develop cardiovascular events as non-hemophilic patients when clotting has been normalized by treatment with factor VIII.

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. Perform assay to determine if factor VIII inhibitor is present. If expected factor VIII activity plasma levels are not attained or if bleeding is not controlled with the expected dose of Helixate FS, use Bethesda Units (BU) to titer inhibitors.
  a. 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.
  b. If inhibitor titers are above 10 BU per mL, adequate hemostasis may not be achieved. The inhibitor titer may rise following Helixate FS infusion as a result of an anamnestic response to factor VIII. The on-demand treatment and control of bleeding in such patients requires the use of alternative therapeutic approaches and agents.

6 ADVERSE REACTIONS
Serious adverse reactions seen with Helixate FS are systemic hypersensitivity reactions, including bronchospastic reactions and/or hypotension and anaphylaxis, and the development of high-titer inhibitors necessitating alternative treatments to factor VIII. The most common adverse reactions (≥4%) observed in clinical trials were 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) associated infections.

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 open-label clinical studies conducted in 73 PTPs, there were 24 adverse reactions reported in the course of 24,936 infusions. Adverse reactions reported by ≥ 4% of the patients are listed in Table 3 below.

### Table 3: Adverse Reactions (AR) in Previously Treated Patients with Frequency of ≥ 4% (Age Range 12–59 years)

<table>
<thead>
<tr>
<th>MedDRA Primary SOC</th>
<th>Preferred Term</th>
<th>N = 73 AR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Rash, pruritus</td>
<td>6 (8.2%)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Infusion site reactions</td>
<td>3 (4.1%)</td>
</tr>
</tbody>
</table>

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

In clinical studies with pediatric PUPs and MTPs, there were 29 adverse reactions reported in the course of 9,389 infusions. Adverse reactions reported by ≥ 4% of the patients are listed in Table 4 below.

### Table 4: Adverse Reactions (AR) in Previously Untreated Patients and Minimally Treated Patients with Frequency of ≥ 4% (Age Range 2–27 months)

<table>
<thead>
<tr>
<th>MedDRA Primary SOC</th>
<th>Preferred Term</th>
<th>N = 61 AR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Rash, pruritus, urticaria</td>
<td>10 (16%)</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Factor VIII inhibition</td>
<td>9 (15%)*</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Infusion site reactions</td>
<td>4 (7%)</td>
</tr>
</tbody>
</table>

**Minimally Treated Patients (MTPs) in the Joint Outcome Study**

In the Joint Outcome Study with pediatric MTPs 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.

### Table 5: Adverse Reactions in Minimally Treated Patients in the Joint Outcome Study (Age Range 0–6 years)

<table>
<thead>
<tr>
<th>MedDRA Primary SOC</th>
<th>Preferred Term</th>
<th>Prophylaxis Arm N = 32 AR (%)</th>
<th>Enhanced Episodic Arm N = 33 AR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical and Medical Procedures</td>
<td>Central venous catheterization, Catheter removal</td>
<td>19 (59%)</td>
<td>18 (55%)*</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Central line infection</td>
<td>6 (19%)</td>
<td>6 (18%)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Pyrexia</td>
<td>1 (3%)</td>
<td>4 (12%)</td>
</tr>
</tbody>
</table>

**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 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). Inhibitor data in PUPs have been collected in several postmarketing registries (see Postmarketing Experience (6.2)).
container and is then lyophilized. The final product does not contain any preservative. It is a sterile, nonpyrogenic powder preparation for intravenous injection. Intravenous administration of sucrose contained in Helixate FS will not affect blood glucose levels.

### Table 6 Stabilizers Contained in Helixate FS Final Container

<table>
<thead>
<tr>
<th>Stabilizer</th>
<th>250 IU, 500 IU, 1000 IU Nominal Vial Sizes</th>
<th>2000 IU, 3000 IU Nominal Vial Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucrose</td>
<td>0.9–1.3%</td>
<td>0.9–1.2%</td>
</tr>
<tr>
<td>Glycine</td>
<td>21–25 mg/mL</td>
<td>20–24 mg/mL</td>
</tr>
<tr>
<td>Histidine</td>
<td>18–23 mmol/L</td>
<td>17–22 mmol/L</td>
</tr>
</tbody>
</table>

Table 7 lists the inactive ingredients/excipients also contained in the final product.

### Table 7 Inactive Ingredients/Excipients

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

### 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 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.

#### 12.3 Pharmacokinetics

The pharmacokinetic properties of Helixate FS were investigated in two separate studies in adult and pediatric previously treated patients (PTPs).

Pharmacokinetic studies with Helixate FS were conducted in 20 PTPs (ages 12 to 33 years) with severe hemophilia A. The pharmacokinetic parameters for Helixate FS were measured in a randomized, crossover clinical trial with the predecessor HELIXATE product using a single dose administration of 50 IU per 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 8).

### Table 8 Pharmacokinetic Parameters for Helixate FS Compared to HELIXATE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Helixate FS</th>
<th>HELIXATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (IU/h/dl)</td>
<td>1588.05 ± 344.32</td>
<td>1879.02 ± 412.32</td>
</tr>
<tr>
<td>Cmax (IU/dl)</td>
<td>114.95 ± 20.19</td>
<td>127.40 ± 33.21</td>
</tr>
<tr>
<td>Half-life (hr)</td>
<td>13.74 ± 1.82</td>
<td>14.07 ± 2.62</td>
</tr>
<tr>
<td>In Vivo Recovery (IU/dl / IU/kg)</td>
<td>2.20 ± 0.34</td>
<td>2.43 ± 0.60</td>
</tr>
</tbody>
</table>

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. The pharmacokinetic parameters are depicted in Table 9.

### 13 NONCLINICAL TOXICOLOGY

#### 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. By inference, the predecessor product HELIXATE 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.

### 13.2 Animal Toxicology and/or Pharmacology

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. Helixate FS has been shown to be comparable to the predecessor product HELIXATE with respect to its biochemical and physiochemical properties, as well as its non-clinical in vivo pharmacology and toxicology.

### 14 CLINICAL STUDIES

#### Previously Treated Patients (PTPs) Clinical Studies

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. A total of 5,684 bleeding episodes were treated during the studies; 92.7% of the bleeds were treated with one (79.7%) or two (13.0%) infusions. Patients could be treated with on-demand or prophylaxis. Regularly scheduled prophylaxis treatment represented 76% of all infusions (treatment regimens of 2–3 infusions per week).

A total of 30 patients received Helixate FS for 41 surgical procedures during the PTP studies. There were both minor and major surgery types, 16 and 25 respectively. Efficacy was based on the attending surgeon’s assessment of whether or not additional AHF was needed. Hemostasis was rated as satisfactory (“excellent” or “good”) in all cases.

#### Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs) Clinical Study

Helixate FS has been used in the treatment of bleeding episodes in pediatric PUPs and 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; the bleeds were treated with one (73%) or two (15%) infusions. A total of 27 surgical procedures were performed in 22 patients during the PUPs and MTPs study. There were both minor and major surgery types, 21 and 6 respectively. The attending surgeon measured efficacy and assigned a rating to the hemostatic outcome according to 4 categories: "excellent (blood loss less than expected),” “good (blood loss as expected),” “moderate (blood loss more than expected),” or “none (uncontrolled bleeding).” Hemostasis was rated as satisfactory (“excellent” or “good”) in all cases.

#### Adult Prophylaxis for Bleeding Frequency Reduction

An ongoing, 3-year, multicenter, open-label, parallel-group, prospective, randomized, controlled clinical study of the effect of routine prophylaxis with Helixate FS versus on-demand use on bleeding frequency in adults and adolescents included 84 PTPs with severe Hemophilia A (FVIII level ≤1 IU/dL), age 15 to 50 years. Patients were matched at baseline on demographic and disease characteristics. The median number of bleeds in the year before enrollment was 18.

Patients were randomized 1:1 to prophylaxis (25 units per kg three times a week) or on-demand use of Helixate FS. Escalation of the prophylaxis dose by 5 units per kg/infusion after years 1 and 2, up to a maximum of 35 units per kg/infusion, was allowed. Bleeding frequency was analyzed in the intent-to-treat population after a median follow-up period of 1.4 years. Patients who received prophylaxis experienced statistically significantly fewer bleeding episodes (p < 0.0001) compared to patients treated on-demand regardless of baseline subgroups examined including age, bleeding history, and presence or absence of target joints. The median number of bleeding episodes was 15.2 times as many bleeds compared to patients treated with prophylaxis. The median annualized bleed rates (bleeds/subject/year) were 37 in the on-demand group versus 2 in the prophylaxis group. The median annualized bleed rate (bleeds/subject/year) in the on-demand group was 33 versus zero in the prophylaxis group. Most of the bleeding occurred in joints: the median joint bleed rate (joints/bleeds/subject/year) in the on-demand group was 24 in the on-demand group versus zero in the prophylaxis group. The mean annualized joint bleed rate was 29 in the on-demand group versus 2 in the prophylaxis group. A total of 5,684 infusions were treated up to 54 months in open label studies with Helixate FS. 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; the bleeds were treated with one (73%) or two (15%) infusions. A total of 27 surgical procedures were performed in 22 patients during the PUPs and MTPs study. There were both minor and major surgery types, 21 and 6 respectively. The attending surgeon measured efficacy and assigned a rating to the hemostatic outcome according to 4 categories as described above for PTPs. Hemostasis was rated as satisfactory (“excellent” or “good”) in all cases.

#### Pediatric Prophylaxis for 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.1 Patients received either 25 IU per kg every other day (primary prophylaxis; n = 32) or at least 3 doses totaling a minimum of 80 IU per kg at the time of a bleeding episode (enhanced prophylactic; 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 hemorhages for subjects on episodic therapy was 4.89 bleed per year, versus 0.63 bleed 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 10 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.,25 and X-rays were scored using the method of Pettersson et al.21 Both scales have been assessed by MRI, or either MRI or radiography, using predefined criteria (described below) in previously untreated UK children with severe hemophilia A, 2000-2011. Blood 84(3):176-87, 2003.

Table 10 Subjects with Joint Damage (Subjects with Available Baseline and Endpoint Data)
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 treat and control bleeding in adults and children with hemophilia A. Your healthcare provider may give you Helixate FS when you have surgery. Helixate FS can reduce the risk of joint damage in children. Helixate FS is not used to treat von Willebrand 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 non-prescription medicines, such as over-the-counter medicines, supplements, or herbal remedies.
Tell your healthcare provider if you have been told you have heart disease or are at risk for heart disease.
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 that 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.
Store Helixate FS at +2°C to +8°C (36°F to 46°F) for up to 30 months from the date of manufacture. Within this period, Helixate FS may be stored for a period of up to 12 months at temperatures up to +25°C or 77°F.
Record the starting date of room temperature storage on the unopened product carton. Once stored at room temperature, do not return the product to the refrigerator. The product then expires after storage at room temperature, or after the expiration date on the product vial, whichever is earlier. 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 procedure. Use only the components for reconstitution and administration that are provided with each package of Helixate FS. If a package is opened or damaged, do not use this component. If these components cannot be used, please contact your healthcare provider. If you have any questions about Helixate FS contact CSL Behring Customer Support 1-800-683-1288.

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).

![Fig. 1](image)

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).

![Fig. 2](image)

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).

![Fig. 3](image)

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.

![Fig. 4](image)
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.

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. 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).

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.

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

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Distributed by:
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