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Pathway
Purchasing Network

# CSL Behring

Dear Healthcare Professional:

We're writing to inform you that the Factor VIII therapy Helixate® FS, Antihemophilic Factor (Recombinant), will no longer be manufactured after December 2017; however, we anticipate that some supply may be available until the middle of 2018. We recognize that Helixate FS has been an important part of your patients' lives, and want to share the rationale behind this decision so you can appropriately advise them.

As a patient-focused company, CSL Behring strives to create innovative therapies for the hemophilia community. That's why we've developed long-lasting AFSTYLA®, Antihemophilic Factor (Recombinant), Single Chain, a next-generation Factor VIII therapy.

With twice-weekly dosing available,* AFSTYLA is the first and only recombinant Factor VIII that delivers proven, long-lasting bleed protection with a novel single-chain design. AFSTYLA also delivered zero bleeds (median AsBR†) in all studied populations regardless of dosing regimen.

With AFSTYLA, all the support services your patients have come to rely on and trust with Helixate FS will remain in place. AFSTYLA also uses the Mix2Vial® system, which will keep their reconstitution process consistent.

As you evaluate the next steps in your Helixate FS patients' therapy, we encourage you to consider AFSTYLA.

CSL Behring has provided Helixate FS to patients for over two decades and we're committed to keeping you up to date with information on this important product going forward. If you have additional questions, a variety of resources are at your disposal:

- Contact your CSL Behring Representative
- Visit AFSTYLA.com for more information and to sign up for updates
- Contact a My Source℠ Care Coordinator at 1-800-676-4266 Monday–Friday, 8 AM to 8 PM ET

**Please see Important Safety Information on pages 2–3 and accompanying full prescribing information for Helixate FS and AFSTYLA.**

Sincerely,

Dr. Jerry Powell

Senior Medical Director, CSL Behring

*FDA-approved for dosing 2 or 3 times a week.
†Annualized spontaneous bleeding rate in clinical trials (IQR=0–2.4 for patients ≥12 years; 0–2.2 for patients <12 years).

## *Our Commitment*

As with every therapy CSL Behring develops, AFSTYLA has the weight of our rigorous standards of quality behind it. Each step of the manufacturing process reflects that long-standing commitment to quality and safety.

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## *Important Safety Information for Helixate FS*

Helixate® FS, Antihemophilic Factor (Recombinant), is 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 prophylactic treatment to reduce the frequency of bleeding episodes in children with hemophilia A and to reduce the risk of joint damage in children without preexisting joint damage.
- Routine prophylactic treatment to reduce the frequency of bleeding episodes in adults with hemophilia A.

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

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.

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. Discontinue Helixate FS if symptoms occur and seek immediate emergency treatment.

Neutralizing antibodies (inhibitors) have been reported following administration of Helixate FS predominately in previously untreated patients. 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.

Hemophilic patients with cardiovascular risk factors or diseases may be at the same risk of developing cardiovascular events as non-hemophilic patients when clotting has been normalized by treatment with factor VIII.

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 and minimally treated patients, skin-related hypersensitivity reactions, infusion-site reactions, and central venous access device (CVAD) associated infections.

**Please see accompanying full prescribing information for Helixate FS.**

## *Important Safety Information for AFSTYLA*

AFSTYLA®, Antihemophilic Factor (Recombinant), Single Chain, is indicated in adults and children with hemophilia A (congenital Factor VIII deficiency) for:

- On-demand treatment and control of bleeding episodes
- Routine prophylaxis to reduce frequency of bleeding episodes
- Perioperative management of bleeding

AFSTYLA is not indicated for the treatment of von Willebrand disease.

**Important Safety Information continues on page 3.**

CSL Behring

## *Important Safety Information for AFSTYLA (cont.)*

AFSTYLA is contraindicated in patients who have had life-threatening hypersensitivity reactions to AFSTYLA or its excipients, or to hamster proteins.

AFSTYLA is for intravenous use only. AFSTYLA can be self-administered or administered by a caregiver with training and approval from a healthcare provider or hemophilia treatment center. Higher and/or more frequent dosing may be needed for patients under 12 years of age.

Hypersensitivity reactions, including anaphylaxis, are possible. Advise patients to immediately report symptoms of a hypersensitivity reaction. If symptoms occur, discontinue AFSTYLA and administer appropriate treatment.

Development of Factor VIII (FVIII) neutralizing antibodies (inhibitors) can occur. If expected FVIII activity levels are not attained or bleeding is not controlled with appropriate dose, perform an assay to measure FVIII inhibitor concentration.

Monitor plasma FVIII activity using a chromogenic assay or one-stage clotting assay. **If one-stage clotting assay is used, multiply result by a conversion factor of 2 to determine FVIII activity level.**

The most common adverse reactions reported in clinical trials (>0.5%) were dizziness and hypersensitivity.

**Please see accompanying full prescribing information for AFSTYLA.**

**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**

**----------INDICATIONS AND USAGE----------**

Helixate FS is an Antihemophilic Factor (Recombinant) 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.

**----------DOSAGE AND ADMINISTRATION----------**

**For intravenous use only.**
Each vial of Helixate FS contains the labeled amount of recombinant factor VIII in international units (IU, unit).
**Control of bleeding episodes and perioperative management (2.1):**
- Dose (units) = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)
- Titrate doses to patient's clinical response.
- Determine treatment frequency based on type of bleeding episode.

**For routine prophylaxis in adults:** 25 units per kg three times a week (2.1).
**For routine prophylaxis in children:** 25 units per kg every other day (2.1).

**----------DOSAGE FORMS AND STRENGTHS----------**

Available as lyophilized powder in single use vials containing nominally 250, 500, 1000, 2000, and 3000 IU (3).

**----------CONTRAINDICATIONS----------**

Do not use in patients who have life-threatening hypersensitivity reactions, including anaphylaxis to mouse or hamster protein or other constituents of the product (4).

**----------WARNINGS AND PRECAUTIONS----------**

- Hypersensitivity reactions, including anaphylaxis, are possible. Should symptoms occur, discontinue treatment with Helixate FS and administer appropriate treatment (5.1).
- Development of activity-neutralizing antibodies can occur in patients receiving factor VIII-containing products, including Helixate FS. 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 (5.2).
- When clotting is normalized by treatment with factor VIII, development of cardiovascular risk factors may be the same as the risk for non-hemophilic patients (5.3).
- Monitor plasma factor VIII levels during infusions when indicated (5.4).

**----------ADVERSE REACTIONS----------**

The most common adverse reactions (≥4%) in clinical trials are inhibitor formation (neutralizing antibodies) 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) 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 may occur in children (4.4–16 years). Dose adjustment may be needed (8.4).

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

**Revised: 5/2016**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed

**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 (rFVIII) 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:

**Dosage (units) = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)**

**or**

**IU/dL (or % normal) = Total Dose (IU)/body weight (kg) x 2 [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**

| Type of Bleeding Episodes | Factor VIII Level Required (IU/dL or % of normal) | Dose (IU/kg) | Frequency of Doses (hours) | Duration of Therapy (days) |
|---|---|---|---|---|
| **Minor**<br>Early hemarthrosis, minor muscle or oral bleeds. | 20 – 40 | 10 – 20 | Repeat dose if there is evidence of further bleeding. | Until bleeding is resolved |
| **Moderate**<br>Bleeding into muscles, bleeding into the oral cavity, definite hemarthroses, and known trauma. | 30 – 60 | 15 – 30 | 12 – 24 | Until bleeding is resolved |
| **Major**<br>Gastrointestinal bleeding.<br>Intracranial, intra-abdominal or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces, or iliopsoas sheath.<br>Fractures.<br>Head trauma. | 80 – 100 | Initial: 40 – 50<br>Repeat: 20 – 25 | 8 – 12 | Until bleeding is resolved |

*Perioperative Management of Bleeding*

A guide for dosing Helixate FS during surgery (perioperative management) is provided in Table 2. The goal of treatment is to maintain a plasma factor VIII activity level at or above the plasma level (in % of normal or in IU/dL) outlined in Table 2.

**Table 2 Dosing for Perioperative Management**

| Type of Surgery | Factor VIII Level Required (IU/dL or % of normal) | Dose (IU/kg) | Frequency of Doses (hours) | Duration of Therapy (days) |
|---|---|---|---|---|
| **Minor**<br>Including tooth extraction | 30 – 60 | 15 – 30 | 12 – 24 | Until bleeding is resolved. |
| **Major**<br>Examples include tonsillectomy, inguinal herniotomy, synovectomy, total knee replacement, craniotomy, osteosynthesis, trauma. | 100 | 50<br>Pre-operatively to achieve 100% activity. | 6 – 12 to keep FVIII activity in desired range | Until healing is complete. |

*Routine Prophylaxis in Adults*

The recommended dose for routine prophylaxis is 25 units per kg of body weight three times per week.

*Routine Prophylaxis in Children*

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

### 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.

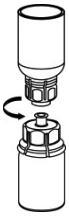
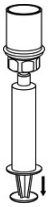
For instructions, patients should follow the recommendations in the FDA-Approved Patient Labeling.

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).<br><br>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). |  <br>Fig. 1<br>  <br>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). |  <br>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. |  <br>Fig. 4 |
| 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. |  <br>Fig. 5 |
| 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) |  <br>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). |  <br>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. |  <br>Fig. 8 |
| 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, glycine, histidine, sodium, calcium chloride, polysorbate 80, imidazole, tri-n-butyl phosphate, and 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 (MuIgG) 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.[6] 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.
  - o 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.
  - o 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)**

| MedDRA Primary SOC | Preferred Term | N = 73 AR (%) |
|---|---|---|
| Skin and Subcutaneous Tissue Disorders | Rash, pruritus | 6 (8.2%) |
| General Disorders and Administration Site Conditions | Infusion site reactions | 3 (4.1%) |

**SOC = System Organ Class**

***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)**

| MedDRA Primary SOC | Preferred Term | N = 61 AR (%) |
|---|---|---|
| Skin and Subcutaneous Tissue Disorders | Rash, pruritus, urticaria | 10 (16%) |
| Blood and Lymphatic System Disorders | Factor VIII inhibition (neutralizing antibodies) | 9 (15%)* |
| General Disorders and Administration Site Conditions | Infusion site reactions | 4 (7%) |

**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 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)**

| MedDRA Primary SOC | Preferred Term | Prophylaxis Arm N = 32 AR (%) | Enhanced Episodic Arm N = 33 AR (%) |
|---|---|---|---|
| **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 titer[1] (> 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 titer[1] (> 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)]*.

The detection of antibody formation is dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Helixate FS with the incidence of antibodies to other products may be misleading.

### 6.2 Postmarketing Experience

Because adverse 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. The following adverse reaction has been identified during post approval use of Helixate FS:

Sensory System – Dysgeusia

**Immunogenicity – Postmarketing Registries**

Data from the Research of Determinants of Inhibitor Development (RODIN) study[7], French National Registry (FranceCoag)[8] and United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO)[9] registry reported an inhibitor development rate in PUPs for Hexliate FS of 38%, 50% and 35%, respectively, which is comparable to previously-reported inhibitor rates[10] for FVIII products. These registry studies show a trend towards an increased risk of inhibitor development in PUPs, as compared to the reference rFVIII product. A survey of Canadian hemophilia centers[11] (2005 to 2012) and available data from the European Haemophilia Safety Surveillance (EUHASS)[12] registry from 2009 to 2013, reported an inhibitor development rate in PUPs for Helixate FS of 42% and 31%, respectively, with no statistically significant differences observed across FVIII products.

## 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 reproductive capacity. Helixate FS should be given to a pregnant woman only if clearly 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 Mothers

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 a nursing woman.

### 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 half-life and recovery of factor VIII. This may be due to differences in body composition.[13] Account for this difference in clearance when dosing or following factor VIII levels in the pediatric population [*see Clinical Pharmacology (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.[14] 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.[15-19] 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. These TSE reduction steps include the Fraction II+III separation step for HPPS (6.0 $\log_{10}$) and an anion exchange chromatography step (3.6 $\log_{10}$).

Helixate FS is formulated with the following as stabilizers (*see Table 6)* in the final

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**

| Stabilizer | 250 IU, 500 IU, 1000 IU Nominal Vial Sizes | 2000 IU, 3000 IU Nominal Vial Sizes |
|---|---|---|
| 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 |

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

**Table 7 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 |

## 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**

| 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 |

The pharmacokinetics of Helixate FS were investigated in pediatric PTPs (4.4–18.1 years of age, average age 12).[13] 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.

**Table 9 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

### 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 measured by the attending surgeon based on a comparison of estimated blood loss from experience with non-hemophilic patients undergoing similar procedures. The surgeon or treating physician 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.

### *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 as described above for PTPs. 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 bleeds ($p<0.0001$) compared to patients treated on-demand regardless of baseline subgroups examined including age, bleeding history, and presence or absence of target joints. The ratio of the mean bleeding frequency was 15.2 (95% CI: 8.5, 27.2; $p<0.0001$) for on-demand versus prophylaxis, indicating that patients who received on-demand treatment experienced on average 15.2 times as many bleeds compared to patients treated with prophylaxis. The mean 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 (joint bleeds/subject/year) 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.

Twenty-two of 42 (52%) prophylaxis subjects experienced no bleeding, and 12 of 42 (29%) prophylaxis subjects experienced only 1–2 bleeds during the follow-up period.

Among prophylaxis patients the mean number of infusions/week was 2.8, and the median dose per prophylaxis infusion was 26 units per kg.

### *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.[5] 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 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 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.,[20] and X-rays were scored using the method of Pettersson et al.[21] 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 10 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.*

## 15 REFERENCES


1. White GC, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J, for the Factor VIII and Factor IX Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definitions in hemophilia. *Thromb Haemost* 85:560-75, 2001.
2. Abildgaard CF, Simone JV, Corrigan JJ, et al: Treatment of hemophilia with glycine-precipitated Factor VIII. *N Engl J Med* 275(9):471–5, 1966.
3. Schwartz RS, Abildgaard CF, Aledort LM, et al: Human recombinant DNA-derived antihemophilic factor (factor VIII) in the treatment of hemophilia A. Recombinant Factor VIII Study Group. *N Engl J Med* 323(26):1800-5, 1990.
4. White GC 2nd, Courter S, Bray GL, et al: A multicenter study of recombinant factor VIII (Recombinate) in previously treated patients with hemophilia A. The Recombinate Previously Treated Patient Study Group. *Thromb Haemost* 77(4):660-667, 1997.
5. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007;357(6):535-44.
6. Kasper CK: Complications of hemophilia A treatment: factor VIII inhibitors. *Ann NY Acad Sci* 614:97-105, 1991.
7. Gouw SC, van den Berg HM, et al: Intensity of factor VIII treatment and inhibitor development in children with severe hemophilia A: the RODIN study. *Blood* 121(20): 4046-4055, 2013.
8. Calvez T, Chambost H, et al: Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A. *Blood* 124(23): 3398-3408, 2014.
9. Collins PW, Palmer BP, et al: Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011. *Blood* 124(23): 3389-3397, 2014.
10. Franchini M, Coppola A, et al: Systematic Review of the Role of FVIII Concentrates in Inhibitor Development in Previously Untreated Patients with Severe Hemophilia A: *A 2013 Update. Semin Throm Hemost* (39): 752-766, 2013.
11. Vezina C, Carcao M, et al: Incidence and risk factors for inhibitor development in previously untreated severe haemophilia A patients born between 2005 and 2010. *Haemophilia* 20(6): 771-776, 2014.
12. Fisher K, Lassila, R, et al. Inhibitor development in haemophilia according to concentrate: Four-year results from the European HAemophilia Safety Surveillance (EUHASS) project. *Thromb Haemost* 113.4, 2015.
13. Barnes C, Lillicrap D, Pazmino-Canizares J, et al: Pharmacokinetics of recombinant factor VIII (Helixate-FS®) in children and causes of inter-patient pharmacokinetic variability. *Haemophilia* 12 (Suppl. 4): 40-49, 2006.
14. Lawn RM, Vehar GA: The molecular genetics of hemophilia. *Sci Am* 254(3):48–54, 1986.
15. Stenland CJ, et al: Partitioning of human and sheep forms of the pathogenic prion protein during the purification of therapeutic proteins from human plasma. *Transfusion* 42(11):1497-500, 2002.
16. Lee DC, Miller JL, Petteway SR: Pathogen safety of manufacturing processes for biological products: special emphasis on HELIXATE® Bayer. *Haemophilia* 8(Suppl. 2):6-9, 2002.
17. Lee DC, Stenland CJ, Miller JL, et al: A direct relationship between the partitioning of the pathogenic prion protein and transmissible spongiform encephalopathy infectivity during the purification of plasma proteins. *Transfusion* 41(4):449-55, 2001.
18. Cai K, Miller JL, Stenland CJ, et al: Solvent-dependent precipitation of prion protein. *Biochim Biophys Acta* 1597(1):28-35, 2002.
19. Trejo SR, Hotta JA, Lebing W, et al: Evaluation of virus and prion reduction in a new intravenous immunoglobulin manufacturing process. *Vox Sang* 84(3):176-87, 2003.
20. Nuss R, Kilcoyne RF, Geraghty S, et al: MRI findings in haemophilic joints treated with radiosynoviorthesis with development of an MRI scale of joint damage. *Haemophilia* 6:162-169, 2000.
21. Pettersson H, Ahlberg A, Nilsson IM: A radiologic classification of hemophilia arthropathy. *Clin Orthop Relat Res* 149:153-159, 1980.


## 16 HOW SUPPLIED/STORAGE AND HANDLING

*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 are provided in the kit.

| 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. Use the actual potency as indicated on the vial label to calculate the dose.

*Storage and Handling*

The product vial and diluent vial are not made with natural rubber latex.

*Product as Packaged for Sale*

- 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 shelf-life then expires after storage at room temperature, or after the expiration date on the product vial, whichever is earlier.
- 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

- After reconstitution, store the Helixate FS solution at room temperature and administer within 3 hours.

## 17 PATIENT COUNSELING INFORMATION

- Advise the patient to read the FDA-approved patient labeling (Patient Information 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.
- 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.

***FDA-Approved Patient Labeling***

Patient Information

**Helixate FS (he-liks-āt)**

**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 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 number of bleeding episodes when used regularly (prophylaxis). 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.

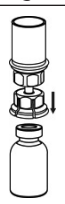
Your healthcare provider may need to take blood tests from time to time.

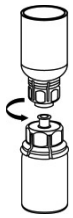
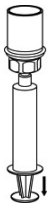
Talk to your healthcare provider before traveling. You should plan to bring enough Helixate FS for your treatment during this time.

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).<br><br>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). |  <br>Fig. 1<br>  <br>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). |  <br>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. |  <br>Fig. 4 |

| | | |
|---|---|---|
| 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. |  Fig. 5 |
| 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). |  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). |  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. |  Fig. 8 |

| | | |
|---|---|---|
| 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:
CSL Behring LLC Kankakee, IL 60901 USA

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

**AFSTYLA®, Antihemophilic Factor (Recombinant), Single Chain**
**For Intravenous Injection, Powder and Solvent for Injection**
**Initial U.S. Approval: 2016**

**----------INDICATIONS AND USAGE----------**

AFSTYLA®, Antihemophilic Factor (Recombinant), Single Chain, is a recombinant, antihemophilic factor indicated in adults and children with hemophilia A (congenital Factor VIII deficiency) for:

- On-demand treatment and control of bleeding episodes,
- Routine prophylaxis to reduce the frequency of bleeding episodes,
- Perioperative management of bleeding.

Limitation of Use

AFSTYLA is not indicated for the treatment of von Willebrand disease (1).

**----------DOSAGE AND ADMINISTRATION----------**

**For intravenous use after reconstitution only.**

- Each vial of AFSTYLA is labeled with the amount of recombinant Factor VIII in international units (IU or unit). One unit per kilogram body weight will raise the Factor VIII level by 2 IU/dL. (2.1)
- Plasma Factor VIII levels can be monitored using either a chromogenic assay or a one-stage clotting assay – routinely used in US clinical laboratories. **If the one-stage clotting assay is used, multiply the result by a conversion factor of 2 to determine the patient's Factor VIII activity level.** (**2.1**, **5.3**)

Calculating Required Dose: (2.1)

Dose (IU) = Body Weight (kg) x Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

**Routine Prophylaxis: (2.1)**

- Adults and adolescents (≥12 years): The recommended starting regimen is 20 to 50 IU per kg of AFSTYLA administered 2 to 3 times weekly.
- Children (<12 years): The recommended starting regimen is 30 to 50 IU per kg of AFSTYLA administered 2 to 3 times weekly. More frequent or higher doses may be required in children <12 years of age to account for the higher clearance in this age group.
- The regimen may be adjusted based on patient response.

**Perioperative Management: (2.1)**

- Ensure the appropriate Factor VIII activity level is achieved and maintained.

**----------DOSAGE FORMS AND STRENGTHS----------**

AFSTYLA is available as a white or slightly yellow lyophilized powder supplied in single-use vials containing nominally 250, 500, 1000, 2000, or 3000 International Units (IU). (3)

**----------CONTRAINDICATIONS----------**

Do not use in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis to AFSTYLA or its excipients, or hamster proteins. (4)

**----------WARNINGS AND PRECAUTIONS----------**

- Hypersensitivity reactions, including anaphylaxis, are possible. Should symptoms occur, immediately discontinue AFSTYLA and administer appropriate treatment. (5.1)
- Development of Factor VIII neutralizing antibodies (inhibitors) can occur. If expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures Factor VIII inhibitor concentration. (5.2)
- If the one-stage clotting assay is used, multiply the result by a conversion factor of 2 to determine the patient's Factor VIII activity level. (5.3)

**----------ADVERSE REACTIONS----------**

**The most common adverse reactions reported in clinical trials (>0.5% of subjects) were dizziness and hypersensitivity. (6)**

**To report SUSPECTED ADVERSE REACTIONS, contact the 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----------**

- Pediatric: Clearance (based on per kg body weight) is higher in pediatric patients 0 to <12 years of age. Higher and/or more frequent dosing may be needed. (8.4)

**See 17 for Patient Counseling Information and FDA-approved Patient Labeling.**

**Issued: 5/2016**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



*** Sections or subsections omitted from the full prescribing information are not listed**

**CSL Behring**
**FULL PRESCRIBING INFORMATION**

# AFSTYLA®

# Antihemophilic Factor (Recombinant), Single Chain

## For Intravenous Injection, Powder and Solvent for Injection

### 1 INDICATIONS AND USAGE

AFSTYLA®, Antihemophilic Factor (Recombinant), Single Chain is a recombinant, antihemophilic factor indicated in adults and children with hemophilia A (congenital Factor VIII deficiency) for:

- On-demand treatment and control of bleeding episodes,
- Routine prophylaxis to reduce the frequency of bleeding episodes,
- Perioperative management of bleeding.

Limitation of Use

AFSTYLA is not indicated for the treatment of von Willebrand disease.

### 2 DOSAGE AND ADMINISTRATION

**For intravenous use after reconstitution only.**

#### 2.1 Dosing Guidelines

- Dose 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.
- Each vial of AFSTYLA states the actual amount of Factor VIII activity in International Units (IU) as determined by chromogenic assay. One IU corresponds to the activity of Factor VIII contained in 1 milliliter (mL) of normal human plasma.
- Plasma Factor VIII levels can be monitored using either a chromogenic assay or a one-stage clotting assay – routinely used in US clinical laboratories. If the one-stage clotting assay is used, multiply the result by a conversion factor of 2 to determine the patient's Factor VIII activity level [see *Warnings and Precautions (5.3)*].

Calculating Required Dose

- The calculation of the required dose of Factor VIII is based on the empirical finding that 1 IU Factor VIII per kg body weight raises the plasma Factor VIII level by 2 IU/dL. The expected in vivo peak increase in Factor VIII level expressed as IU/dL (or % of normal) is estimated using the following formula:

**Estimated Increment of Factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)**

The dose to achieve a desired in vivo peak increase in Factor VIII level may be calculated using the following formula:

**Dose (IU) = body weight (kg) x Desired Factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)**

The amount of AFSTYLA to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

On-demand Treatment and Control of Bleeding Episodes

A guide for dosing AFSTYLA in the treatment and control of bleeding episodes is provided in Table 1. Consideration should be given to maintaining a Factor VIII activity at or above the target range.

**Table 1. Dosing for On-demand Treatment and Control of Bleeding Episodes**

| Type of Bleeding Episode | Factor VIII Activity Level Required (% or IU/dL) | Frequency of Doses (hours) |
|---|---|---|
| **Minor** Uncomplicated hemarthrosis, minor muscle bleeding or oral bleeding | 20-40 | Repeat injection every 12-24 hours until the bleeding is resolved. |
| **Moderate** Muscle bleeding (except iliopsoas), hemarthrosis, or mild trauma | 30-60 | Repeat injection every 12-24 hours until the bleeding is resolved. |
| **Major/Life-threatening** Limb threatening hemorrhage, deep muscle bleeding (including iliopsoas), intracranial and retropharyngeal bleeding, fractures or head trauma | 60-100 | Repeat injection every 8-24 hours until bleed is resolved. |

Routine Prophylaxis

- Adults and adolescents (≥12 years): The recommended starting regimen is 20 to 50 IU per kg of AFSTYLA administered 2 to 3 times weekly.
- Children (<12 years): The recommended starting regimen is 30 to 50 IU per kg of AFSTYLA administered 2 to 3 times weekly. More frequent or higher doses may be required in children <12 years of age to account for the higher clearance in this age group [see *Clinical Pharmacology (12.3)*].
- The regimen may be adjusted based on patient response.

Perioperative Management of Bleeding

A guide for dosing AFSTYLA during surgery (perioperative management of bleeding) is provided in Table 2. Consideration should be given to maintaining a Factor VIII activity at or above the target range.

**Table 2. Target Factor VIII Activity Levels for Perioperative Management of Bleeding**

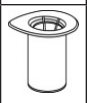
| Type of Surgery | Factor VIII Activity Level Required (% or IU/dL) | Frequency of Doses (hours) / Duration of Therapy (days) |
|---|---|---|
| **Minor** (including tooth extraction) | 30-60 | Repeat injection every 24 hours for at least 1 day, until healing is achieved. |
| **Major** (intracranial, intra-abdominal, intrathoracic, or joint-replacement) | 80-100 | Repeat injection every 8-24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a Factor VIII activity of 30-60% (IU/dL). |

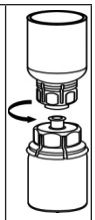
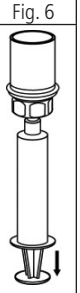
#### 2.2 Preparation and Reconstitution

- Reconstitute AFSTYLA using aseptic technique with diluent provided in the kit.
- Visually inspect the reconstituted solution for particulate matter prior to administration. The solution should be free from visible particles. Do not use if particulate matter is observed.

The procedures provided in Table 3 are general guidelines for the preparation and reconstitution of AFSTYLA.

**Table 3. AFSTYLA Reconstitution Instructions**

| | | |
|---|---|---|
| 1. | Ensure that the AFSTYLA vial and diluent vial are at room temperature. Prepare and administer using aseptic technique. | |
| 2. | Place the AFSTYLA vial, diluent vial, and Mix2Vial® transfer set on a flat surface. | |
| 3. | Remove AFSTYLA and diluent vial flip caps. Wipe the stoppers with the sterile alcohol swab provided and allow the stoppers to dry prior to opening the Mix2Vial transfer set package. | |
| 4. | Open the Mix2Vial transfer set package by peeling away the lid (Fig. 1). Leave the Mix2Vial transfer set in the clear package. |  Fig. 1 |
| 5. | Place the diluent vial on a flat surface and hold the vial tightly. Grip the Mix2Vial transfer set together with the clear package and push the plastic spike at the blue end of the Mix2Vial transfer set firmly through the center of the stopper of the diluent vial (Fig. 2). |  Fig. 2 |
| 6. | Carefully remove the clear package from the Mix2Vial transfer set. Make sure that you pull up only the clear package, not the Mix2Vial transfer set (Fig. 3). |  Fig. 3 |
| 7. | With the AFSTYLA vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and push the plastic spike of the transparent adapter firmly through the center of the stopper of the AFSTYLA vial (Fig. 4). The diluent will automatically transfer into the AFSTYLA vial. |  Fig. 4 |
| 8. | With the diluent and AFSTYLA vial still attached to the Mix2Vial transfer set, gently swirl the AFSTYLA vial to ensure that the AFSTYLA is fully dissolved (Fig. 5). Do not shake the vial. |  Fig. 5 |

| | |
|---|---|
| 9. With one hand, grasp the AFSTYLA side of the Mix2Vial transfer set and with the other hand grasp the blue diluent-side of the Mix2Vial transfer set, and unscrew the set into two pieces. (Fig. 6). |  Fig. 6 |
| 10. Draw air into an empty, sterile syringe. While the AFSTYLA vial is upright, screw the syringe to the Mix2Vial transfer set. Inject air into the AFSTYLA 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). |  Fig. 7 |
| 11. Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the plunger facing down) and unscrew the syringe from the Mix2Vial transfer set (Fig. 8). |  Fig. 8 |
| 12. After reconstitution, infuse immediately or within 4 hours. Reconstituted AFSTYLA may be stored at room temperature, not to exceed 25°C (77°F), for up to 4 hours. Do not freeze. Protect from direct sunlight. | |
| 13. Record treatment - Remove the peel-off portion of the label from each vial used, and affix it to the patient's treatment diary/log book or scan the vial if recording the infusion electronically. | |
| 14. If the dose requires more than one vial, use a separate, unused Mix2Vial® transfer set for each product vial. Repeat step 10 to pool the contents of the vial into one syringe. | |

**2.3 Administration**

- Use aseptic technique when administering AFSTYLA.
- Do not mix AFSTYLA with other medicinal products.
- Administer by intravenous injection. The rate of administration should be determined by the patient's comfort level. Do not exceed infusion rate of 10 mL per minute.
- Administer AFSTYLA at room temperature within 4 hours after reconstitution.
- AFSTYLA is for single use only. Following administration, discard any unused solution and all administration equipment in an appropriate manner as per local requirements.
- If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteremia and catheter site thrombosis should be considered.

## 3 DOSAGE FORMS AND STRENGTHS

AFSTYLA is available as a white or slightly yellow lyophilized powder supplied in single-use vials containing nominally 250, 500, 1000, 2000, or 3000 IU. The actual potency is labeled on each AFSTYLA vial and carton.

## 4 CONTRAINDICATIONS

AFSTYLA is contraindicated in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis to AFSTYLA or its excipients (e.g., polysorbate 80) *[see Description (11)]*, or hamster proteins *[see Warnings and Precautions (5.1)]*.

## 5 WARNINGS AND PRECAUTIONS

**5.1 Hypersensitivity Reactions**

Allergic-type hypersensitivity reactions, including anaphylaxis, are possible with AFSTYLA. Inform patients of the early signs of hypersensitivity reactions that may progress to anaphylaxis (including hives, generalized urticaria, tightness of the chest, wheezing, hypotension and pruritus). Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur.

For patients with previous hypersensitivity reactions, consider premedication with antihistamines.

**5.2 Neutralizing Antibodies**

Formation of neutralizing antibodies (inhibitors) to Factor VIII can occur following administration of Factor VIII products. Monitor patients for the development of neutralizing antibodies (inhibitors) by appropriate clinical observations and laboratory tests. If expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled after AFSTYLA administration, the presence of an inhibitor (neutralizing antibody) should be suspected *[see Warnings and Precautions (5.3)]*.

Contact a specialized hemophilia treatment center if a patient develops an inhibitor.

**5.3 Monitoring Laboratory Tests**

- Monitor plasma Factor VIII activity in patients receiving AFSTYLA using either the chromogenic assay or the one-stage clotting assay, which is routinely used in US clinical laboratories. The chromogenic assay result most accurately reflects the clinical hemostatic potential of AFSTYLA and is preferred. The one-stage clotting assay result underestimates the Factor VIII activity level compared to the chromogenic assay result by approximately one-half. If the one-stage clotting assay is used, multiply the result by a conversion factor of 2 to determine the patient's Factor VIII activity level. Incorrect interpretation of the Factor VIII activity obtained by the one-stage clotting assay could lead to unnecessary additional dosing, higher chronic dosing, or investigations for an inhibitor.
- Monitor for the development of Factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected plasma Factor VIII activity levels are not attained or if bleeding is not controlled with the expected dose of AFSTYLA. Use Bethesda Units (BU) to report inhibitor levels.

## 6 ADVERSE REACTIONS

The most common adverse reactions (>0.5% of subjects) reported in clinical trials were dizziness and hypersensitivity.

**6.1 Clinical Trials Experience**

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

The safety, efficacy and pharmacokinetics of AFSTYLA have been evaluated in 258 previously treated patients (PTPs) with severe hemophilia A (<1% endogenous Factor VIII activity) who received at least one dose of AFSTYLA as part of either routine prophylaxis, on-demand treatment of bleeding episodes or perioperative management in two completed clinical trials (an adult/adolescent study [≥12 to 65 years of age] and a pediatric study [<12 years of age]), and an ongoing extension study (0 to ≤65 years of age). Patients with a history of, or current FVIII inhibitors, or any first order family history of FVIII inhibitors, patients with known hypersensitivity (allergic reaction or anaphylaxis) to any FVIII product or hamster protein, and patients with evidence of thrombosis, including deep vein thrombosis, stroke, pulmonary embolism, myocardial infarction and arterial embolus within 3 months prior to Day 1 of the study were excluded from study participation.

Eighty-four (32.6%) subjects were children <12 years of age (35 [13.6%] 0 to <6 years and 49 [19.0%] ≥6 to <12 years), 14 (5.4%) were adolescents (≥12 to <18 years), and 160 (62.0%) were adults (≥18 to ≤65 years). There have been a total of 28,418 exposure days (EDs), with at least 28,492 injections of AFSTYLA administered. In the completed studies, a total of 185 subjects achieved at least 50 EDs, of whom 60 subjects achieved ≥100 EDs.

Adverse reactions (ARs) (summarized in Table 4) were reported for 14 of 258 (5.4%) subjects in all studies. An adverse reaction of hypersensitivity resulted in the withdrawal of one subject. No subject developed neutralizing antibodies (inhibitors) to Factor VIII or antibodies to host cell proteins. No events of anaphylaxis or thrombosis were reported.

**Table 4. Adverse Reactions Reported for AFSTYLA (N=258)**

| MedDRA System Organ Class | Adverse Reactions | Number of Subjects n (%) |
|---|---|---|
| **Immune system disorders** | Hypersensitivity | 4 (1.6) |
| **Nervous system disorders** | Dizziness | 2 (0.8) |
| | Paresthesia | 1 (0.4) |
| **Skin and subcutaneous tissue disorders** | Rash | 1 (0.4) |
| | Erythema | 1.(0.4) |
| | Pruritus | 1 (0.4) |
| **General disorders and administration site conditions** | Pyrexia | 1 (0.4) |
| | Injection-site pain | 1 (0.4) |
| | Chills | 1 (0.4) |
| | Feeling hot | 1 (0.4) |

**6.2 Immunogenicity**

All subjects were monitored for inhibitory and binding antibodies to AFSTYLA, and binding antibodies to CHO host cell proteins prior to the first infusion of AFSTYLA, at defined intervals during the studies and at the end of study visit.

No subjects developed neutralizing antibodies (inhibitors) to Factor VIII or antibodies against chinese hamster ovary (CHO) host cell proteins at any time during the clinical studies. Four subjects in the adult/adolescent study and 10 subjects in the pediatric study were negative for non-neutralizing anti-drug antibodies (ADAs) at screening and turned positive during

the clinical study. Two of the adult/adolescent subjects and 3 of the pediatric subjects who developed ADAs were negative at end of study visit. No adverse events were associated with the development of ADAs. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, it may be misleading to compare the incidence of antibodies to AFSTYLA with the incidence of antibodies to other products.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

There are no data with AFSTYLA use in pregnant women to inform on drug-associated risk. No developmental or animal reproduction toxicity studies were conducted with AFSTYLA. Thus, the risk of developmental toxicity including, structural abnormalities, embryo-fetal and/or infant mortality, functional impairment, and alterations to growth is not known. In the US general population, the estimated background risk of major birth defects occurs in 2-4% of the general population and miscarriage occurs in 15-20% of clinically recognized pregnancies. AFSTYLA should be given to a pregnant woman only if clearly needed.

### 8.2 Lactation

Risk Summary

There is no information regarding the excretion of AFSTYLA in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AFSTYLA and any potential adverse effects on the breastfed infant from AFSTYLA or from the underlying maternal condition.

### 8.4 Pediatric Use

Safety and efficacy studies with AFSTYLA have been performed in 98 previously treated pediatric patients <18 years of age. Fourteen adolescent subjects ≥12 to <18 years were enrolled in the adult/adolescent safety and efficacy study. Thirty-five subjects 0 to <6 years and 49 subjects ≥6 to <12 years were enrolled in a pediatric safety and efficacy study *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*. Because clearance (based on per kg body weight) has been shown to be higher in the pediatric population 0 to <12 years, more frequent or higher doses of AFSTYLA based on body weight may be needed *[see Clinical Pharmacology (12.3)]*.

### 8.5 Geriatric Use

Clinical studies of AFSTYLA did not include subjects over 65 years to determine whether or not they respond differently from younger subjects.

## 11 DESCRIPTION

AFSTYLA is a single-chain recombinant Factor VIII produced in chinese hamster ovary (CHO) cells. It is a construct where the B-domain occurring in wild type full-length Factor VIII has been truncated and 4 amino acids of the adjacent acidic a3 domain were removed (amino acids 765 to 1652 of full-length Factor VIII). AFSTYLA is expressed as a single-chain Factor VIII molecule with covalent linkage between heavy and light chains; thereby keeping the molecule in the single chain form resulting in increased stability and increased von Willebrand Factor (VWF) affinity. Except for a new N-glycosylation site at the junction between heavy and light chains, the post-translational modifications are comparable to endogenous Factor VIII.

AFSTYLA is purified by a controlled multi-step process including two virus reduction steps complementing each other in their mode of action. No human or animal derived proteins are used in the purification or formulation processes.

AFSTYLA is a preservative-free, sterile, non-pyrogenic, lyophilized powder to be reconstituted with sterile water for injection (sWFI) for intravenous injection. AFSTYLA is available in single-use vials containing the labeled amount of Factor VIII activity, expressed in IU. Each vial contains nominally 250, 500, 1000, 2000 or 3000 IU of AFSTYLA. The actual potency is labeled on each AFSTYLA vial and carton. After reconstitution of the lyophilized powder, all dosage strengths yield an almost colorless to slightly opalescent solution. The concentrations of excipients based on the vial size, as well as the amount of sWFI for reconstitution are provided in the table below.

**Nominal Composition after Reconstitution with sWFI**

| Ingredient | 250 IU vial | 500 IU vial | 1000 IU vial | 2000 IU vial | 3000 IU vial |
|---|---|---|---|---|---|
| rVIII-Single Chain | 100 IU/mL | 200 IU/mL | 400 IU/mL | 400 IU/mL | 600 IU/mL |
| L-Histidine | 3.1 mg/mL | 3.1 mg/mL | 3.1 mg/mL | 3.1 mg/mL | 3.1 mg/mL |
| Polysorbate 80 | 0.2 mg/mL | 0.2 mg/mL | 0.2 mg/mL | 0.2 mg/mL | 0.2 mg/mL |
| Calcium chloride | 0.4 mg/mL | 0.4 mg/mL | 0.4 mg/mL | 0.4 mg/mL | 0.4 mg/mL |
| Sodium chloride | 16.4 mg/mL | 16.4 mg/mL | 16.4 mg/mL | 16.4 mg/mL | 16.4 mg/mL |
| Sucrose | 6 mg/mL | 6 mg/mL | 6 mg/mL | 6 mg/mL | 6 mg/mL |
| Water for Injection | 2.5 mL | 2.5 mL | 2.5 mL | 5 mL | 5 mL |

The number of units of Factor VIII administered is expressed in IU, which are related to the current WHO standard for Factor VIII products. One IU of Factor VIII activity in plasma is equivalent to that quantity of Factor VIII in 1 mL of normal plasma. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IU (relative to an International Standard for Factor VIII in plasma).

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

AFSTYLA is a recombinant protein that replaces the missing Coagulation Factor VIII needed for effective hemostasis. AFSTYLA is a single polypeptide chain with a truncated B-domain that allows for a covalent bridge to link the Factor VIII heavy and light chains. AFSTYLA has demonstrated a higher VWF affinity relative to full-length rFVIII.[1] VWF stabilizes Factor VIII and protects it from degradation. Activated AFSTYLA has an amino acid sequence identical to endogenous FVIIIa.

### 12.2 Pharmacodynamics

Hemophilia A is an X-linked hereditary disorder of blood coagulation due to decreased levels of Factor VIII and results in bleeding into joints, muscles or internal organs, either spontaneously or as result of accidental or surgical trauma. Replacement therapy increases the plasma levels of Factor VIII enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

### 12.3 Pharmacokinetics

Subjects ≥12 years

The pharmacokinetics (PK) of AFSTYLA were evaluated in 91 (81 adults ≥18 years and 10 adolescents ≥12 to <18 years) previously treated subjects following an intravenous injection of a single dose of 50 IU/kg.

The PK parameters (Table 5) were based on plasma Factor VIII activity measured by the chromogenic assay after the first dose (initial PK assessment). The PK profile obtained 3 to 6 months after the initial PK assessment was comparable with the PK profile obtained after the first dose.

**Table 5. Pharmacokinetic Parameters (Arithmetic Mean, Coefficient of Variation [CV%]) in Adults and Adolescents Following a Single Injection of 50 IU/kg of AFSTYLA - Chromogenic Assay**

| PK Parameters | ≥18 years (N=81) | ≥12 to <18 years (N=10) |
|---|---|---|
| IR (IU/dL)/(IU/kg) | 2.00 (20.8) | 1.69 (24.8) |
| $C_{max}$ (IU/dL) | 106 (18.1) | 89.7 (24.8) |
| $AUC_{0\text{-}inf}$ (IU*h/dL) | 1960 (33.1) | 1540 (36.5) |
| $t_{1/2}$ (h) | 14.2 (26.0) | 14.3 (33.3) |
| MRT (h) | 20.4 (25.8) | 20.0 (32.2) |
| CL (mL/h/kg) | 2.90 (34.4) | 3.80 (46.9) |
| $V_{ss}$ (mL/kg) | 55.2 (20.8) | 68.5 (29.9) |

IR = incremental recovery recorded at 30 minutes after injection; $C_{max}$ = observed maximum plasma concentration; $AUC_{0\text{-}inf}$ = area under the Factor VIII activity time curve extrapolated to infinity; $t_{1/2}$ = half-life; MRT = mean residence time; CL = body weight adjusted clearance; $V_{ss}$ = body weight adjusted volume of distribution at steady-state.

Children <12 years

Pharmacokinetic parameters of AFSTYLA were evaluated in 39 previously treated children (0 to <12 years) in open-label, multicenter studies following a 50 IU/kg intravenous injection of AFSTYLA.

Table 6 summarizes the PK parameters calculated from the pediatric data. These parameters were estimated based on the plasma Factor VIII activity over time profile.

**Table 6. Comparison of Pharmacokinetic Parameters in Children by Age Category (Arithmetic Mean, Coefficient of Variation [CV%]) Following a Single Injection of 50 IU/kg of AFSTYLA - Chromogenic Assay**

| PK Parameters | 0 to <6 years (N=20) | ≥6 to <12 years (N=19) |
|---|---|---|
| IR (IU/dL)/(IU/kg) | 1.60 (21.1) | 1.66 (19.7) |
| $C_{max}$ (IU/dL) | 80.2 (20.6) | 83.5 (19.5) |
| $AUC_{0\text{-}inf}$ (IU*h/dL) | 1080 (31.0) | 1170 (26.3) |
| $t_{1/2}$ (h) | 10.4 (28.7) | 10.2 (19.4) |
| MRT (h) | 12.4 (25.0) | 12.3 (16.8) |
| CL (mL/h/kg) | 5.07 (29.6) | 4.63 (29.5) |
| $V_{ss}$ (mL/kg) | 71.0 (11.8) | 67.1 (22.3) |

IR = incremental recovery recorded at 30 minutes after injection for subjects 12 to < 18 years and at 60 minutes after injection for subjects 1 to <12 years; $C_{max}$ = observed maximum plasma concentration; AUC = area under the Factor VIII activity time curve extrapolated to infinity; $t_{1/2}$ = half-life; MRT = mean residence time; CL = body weight adjusted clearance; $V_{ss}$ = body weight adjusted volume of distribution at steady-state.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies investigating the carcinogenic effects of AFSTYLA have not been conducted. In vitro and in vivo testing of AFSTYLA for mutagenicity or effects on fertility were not performed.

## 14 CLINICAL STUDIES

The safety and efficacy of AFSTYLA were evaluated in two studies: an Open-label, Multicenter, Crossover Safety, Efficacy and Pharmacokinetic Study in adults/adolescents as well as in an Open-label Pharmacokinetic, Efficacy and Safety study in children. These studies characterized the PK of AFSTYLA and determined hemostatic efficacy in the control of bleeding events, the prevention of bleeding events in prophylaxis and in the adult/adolescent study determined hemostatic efficacy during perioperative management of bleeding in subjects undergoing surgical procedures.

The adult/adolescent study enrolled a total of 175 previously treated male subjects with severe hemophilia A (<1% endogenous Factor VIII activity). Subjects ranged in age from 12 to 65 years, including 14 adolescent subjects (≥12 to <18 years). Of the 175 enrolled subjects, 174 received at least one dose of AFSTYLA and 173 (99%) were evaluable for efficacy. A total of 161 subjects (92.5%) completed the study. A total of 120 (69.0%) subjects were treated for at least 50 EDs and 52 (29.9%) of those subjects were treated for at least 100 EDs. Subjects received a total of 14,592 injections with a median of 67.0 (range 1 to 395) injections per subject.

The pediatric study enrolled 84 previously treated male subjects with severe hemophilia A (35 subjects 0 to <6 years and 49 subjects ≥6 to <12 years). Of the 84 enrolled subjects, all received at least one dose of AFSTYLA and 83 (99%) were evaluable for efficacy. A total of 65 (77.4%) subjects were treated for at least 50 EDs and 8 (9.5%) of those subjects were treated for at least 100 EDs. Subjects received a total of 5,313 injections with a median of 59 (range 4 to 145) injections per subject.

On-demand Treatment and Control of Bleeding Episodes

In the adult/adolescent study a total of 848 bleeding episodes were treated with AFSTYLA and 835 received an efficacy assessment by the investigator. The majority of the bleeding episodes occurred in joints. The median dose per injection used to treat a bleeding episode was 31.7 IU/kg (range 6 to 84 IU/kg). Of the 848 bleeding episodes, 686 (81%) were controlled with a single AFSTYLA injection and another 107 (13%) were controlled with 2 injections. Fifty-five (6%) of the 848 bleeding episodes required 3 or more injections. For 94% of bleeding episodes the hemostatic efficacy rating by the investigator was either excellent or good.

In the pediatric study a total of 347 bleeding episodes were treated with AFSTYLA all of which received an efficacy assessment by the investigator. The majority of the bleeding episodes occurred in joints. The median dose per injection used to treat a bleeding episode was 27.3 IU/kg (range 16 to 76 IU/kg). Of the 347 bleeding episodes, 298 (86%) were controlled with a single AFSTYLA injection and another 34 (10%) were controlled with 2 injections. Fifteen (4%) of the 347 bleeding episodes required 3 or more injections. For 96% of bleeding episodes the hemostatic efficacy rating by the investigator was either excellent or good.

Assessment of response to treatment of bleeds by the investigator was as follows:

**Excellent:** Pain relief and/or improvement in signs of bleeding (i.e., swelling, tenderness, and/or increased range of motion in the case of musculoskeletal hemorrhage) within approximately 8 hours after the first infusion

**Good:** Pain relief and/or improvement in signs of bleeding at approximately 8 hours after the first infusion, but requires two infusions for complete resolution

**Moderate:** Probable or slight beneficial effect within approximately 8 hours after the first infusion; requires more than two infusions for complete resolution

**No response:** No improvement at all or condition worsens (i.e., signs of bleeding) after the first infusion and additional hemostatic intervention is required with another FVIII product, cryoprecipitate, or plasma for complete resolution.

Efficacy in control of bleeding episodes in both studies is summarized in Table 7.

**Table 7. Efficacy of AFSTYLA in Control of Bleeding**

| Bleeding Episodes Treated | Adult and Adolescent (≥12 to 65 years of age) (N=848) | Pediatric (0 to <12 years of age) (N=347) |
|---|---|---|
| **Number of injections** | | |
| 1 injection, n (%) | 686 (81%) | 298 (85.9%) |
| 2 injections, n (%) | 107 (13%) | 34 (9.8%) |
| 3 injections, n (%) | 29 (3%) | 8 (2.3%) |
| >3 injections, n (%) | 26 (3%) | 7 (2.0%) |
| **Efficacy evaluation by investigator** | **(N=835)** | **(N=347)** |
| Excellent or Good, n (%) | 783 (94%) | 334 (96.3%) |
| Moderate, n (%) | 52 (6%) | 12 (3.5%) |
| No response, n (%) | 0 | 1 (0.3%) |

Routine Prophylaxis

*Adult and Adolescent Study*

In the adult/adolescent and pediatric studies, subjects received prophylaxis in a regimen that was determined by the investigator, taking into account the subject's Factor VIII treatment regimen used prior to enrollment and the subject's bleeding phenotype.

In the adult/adolescent study, 54% of the 146 subjects on prophylaxis received AFSTYLA 3 times weekly; 32% of subjects received AFSTYLA 2 times weekly; 6% received AFSTYLA every other day, and 8% of subjects received other regimens.

The annualized bleeding rate (ABR) was comparable between subjects on a 3 times weekly regimen (median ABR of 1.53) and those on a 2 times weekly regimen (median ABR of 0.00). The annualized spontaneous bleeding rate (AsBR) was also comparable between subjects on a 3 times weekly regimen (median AsBR of 0.0) and those on a 2 times weekly regimen (median AsBR of 0.0). The number of subjects who needed dose adjustments was comparable between the two groups (34.2% [27 subjects] for three times weekly and 27.7% [13 subjects] for twice weekly).

The median prescribed dose for subjects on a 3 times weekly prophylaxis regimen was 30 IU/kg (12 to 50 IU/kg). The median prescribed dose for subjects on a 2 times weekly regimen was 35 IU/kg (17 to 50 IU/kg).

The ABR in prophylaxis (median of 1.14) was significantly lower ($p < 0.0001$) than the ABR that was observed in subjects treated on-demand (median of 19.64). Sixty-three of 146 subjects (43%) experienced no bleeding episodes while on prophylaxis. There were no severe or life-threatening bleeds (e.g., intracranial hemorrhage) in subjects receiving prophylaxis.

*Pediatric Study*

In the pediatric study, 54% of the 80 subjects on prophylaxis received AFSTYLA 2 times a week; 30% of subjects received AFSTYLA 3 times a week; 4% received AFSTYLA every other day, and 12% of subjects received other regimens.

Twenty-one of 80 subjects (26%) experienced no bleeding episodes while on prophylaxis. There was one severe bleed (hip joint hemorrhage) in the pediatric study that was successfully treated.

For subjects on prophylaxis the overall ABR was 3.69, with a median ABR of 2.30 for subjects on a 3 times a week regimen and 4.37 for subjects on a 2 times a week regimen. The median AsBR (0.00) was identical between subjects on the 3 times a week and 2 times a week regimens.

The median prescribed dose for subjects on a 3 times a week regimen was 32 IU/kg (19 to 50 IU/kg) and for subjects on a 2 times a week regimen was 35 IU/kg (20 to 57 IU/kg).

The ABRs for prophylaxis and on-demand in both studies are summarized in Table 8.

**Table 8. Summary of Annualized Bleeding Rate (ABR) by AFSTYLA Treatment Regimen**

| | Phase I/III Adult/ Adolescent Study | | Phase III Pediatric Study | |
|---|---|---|---|---|
| | Prophylaxis (N=146) | On-demand (N=27) | Prophylaxis (N=80) | On-demand (N=3) |
| Overall ABR Median (IQR*) | 1.14 (0–4.2) | 19.64 (6.2–46.5) | 3.69 (0–7.2) | 78.56 (35.1–86.6) |
| Annualized Spontaneous Bleeding Rate (AsBR) Median (IQR*) | 0 (0–2.4) | 11.73 (2.8–36.5) | 0 (0–2.2) | 31.76 (0–42.7) |
| Number of subjects with zero bleeding episodes | 63 (43.2%) | 1 (3.7%) | 21 (26.3%) | 0 |

* IQR = interquartile range, 25th percentile to 75th percentile

Perioperative Management of Bleeding

Thirteen subjects in the adult/adolescent study underwent a total of 16 surgical procedures. Overall, investigators assessed hemostatic efficacy of AFSTYLA in perioperative management of bleeding as excellent in 15 of 16 surgeries and as good in 1 of 16 surgeries (see Table 9). Median factor consumption pre- and intra-operatively was 89.4 IU/kg (range 40.5 to 108.6 IU/kg).

Assessment of hemostasis during surgical procedures by the investigator was as follows:

**Excellent:** Hemostasis clinically not significantly different from normal (e.g., achieved hemostasis comparable to that expected during similar surgery in a non-factor deficient patient) in the absence of other hemostatic intervention and estimated blood loss during surgery is not more than 20% higher than the predicted blood loss for the intended surgery

**Good:** Normal or mildly abnormal hemostasis in terms of quantity and/or quality (e.g., slight oozing, prolonged time to hemostasis with somewhat increased bleeding compared to a non-factor deficient patient in the absence of other hemostatic intervention) or estimated blood loss is >20%, but ≤30% higher than the predicted blood loss for intended surgery

**Moderate:** Moderately abnormal hemostasis in terms of quantity and/or quality (e.g., moderate hemorrhage that is difficult to control) with estimated blood loss greater than what is defined as good

**Poor/No Response:** Severely abnormal hemostasis in terms of quantity and/or quality (e.g., severe hemorrhage that is difficult to control) and/or additional hemostatic intervention required with another FVIII product, cryoprecipitate, or plasma for complete resolution.

**Table 9. Efficacy of AFSTYLA in Perioperative Management of Bleeding**

| Procedure | Efficacy Evaluation | Factor Consumption (IU/kg) (pre- and intra-operatively) |
|---|---|---|
| Extraction of wisdom teeth | Excellent | 51.09 |
| Abdominal hernia repair | Excellent | 47.89 |
| Elbow replacement | Excellent | 108.58 |
| Ankle arthroplasty | Excellent | 76.83 |
| Knee replacement (5) | Excellent (4), Good (1) | 92.49<br>100.9<br>67.26<br>105.79<br>86.09 |
| Cholecystectomy<br>and<br>Lengthening of the Achilles tendon combined with:<br>Straightening of the right toes | Excellent<br><br>Excellent | 105.95 |
| Circumcision (3) | Excellent (3) | 99.04<br>92.74<br>81.5 |
| Open reduction internal fixation (ORIF) right ankle | Excellent | 89.36 |
| Hardware removal, Right ankle | Excellent | 40.45 |

## 15 REFERENCES

[1] Zollner S, Raquet E, Claar Ph, Müller-Cohrs J, Metzner HJ, Weimer Th, Pragst I, Dickneite G, Schulte S. Non-clinical pharmacokinetics and pharmacodynamics of rVIII-SingleChain, a novel recombinant single-chain factor VIII, Thrombosis Research 2014; 134: 125-131.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

AFSTYLA is supplied in a kit containing a lyophilized powder in a single-use vial labeled with the amount of Factor VIII activity, expressed in international units (IU). Actual Factor VIII activity in International Units (IU) is stated on the AFSTYLA carton and vial label.

AFSTYLA is packaged with Sterile Water for Injection, USP (2.5 mL for reconstitution of 250, 500 or 1000 IU or 5 mL for reconstitution of 2000 or 3000 IU AFSTYLA), one Mix2Vial filter transfer set, and one sterile alcohol swab. Components are not made of natural rubber latex.

| Nominal Strength | Fill Size Color Indicator | Kit NDC |
|---|---|---|
| 250 IU | Orange | 69911-474-02 |
| 500 IU | Blue | 69911-475-02 |
| 1000 IU | Green | 69911-476-02 |
| 2000 IU | Purple | 69911-477-02 |
| 3000 IU | Yellow | 69911-478-02 |

Storage and Handling

- Store AFSTYLA in the original package to protect the AFSTYLA vials from light.
- Store AFSTYLA in powder form at 2°C to 8°C (36°F to 46°F). Do not freeze to avoid damage to the diluent vial. AFSTYLA can be stored at room temperature, not to exceed 25°C (77°F), for a single period of up to 3 months, within the expiration date printed on the carton and vial labels.
- Record the starting date of room temperature on the unopened product carton. Once stored at room temperature, do not return the product to the refrigerator. The shelf-life then expires after storage at room temperature for 3 months, or after the expiration date on the product vial, whichever is earlier.
- Do not use AFSTYLA after the expiration date indicated on the vial.
- The reconstituted product (after mixing dry product with diluent) can be stored at 2°C to 8°C (36°F to 46°F), or at room temperature, not to exceed 25°C (77°F), for up to 4 hours.
- Protect from direct sunlight.
- After reconstitution, if the product is not used within 4 hours, it must be discarded.
- Do not use AFSTYLA if the reconstituted solution is cloudy or has particulate matter.
- Discard any unused AFSTYLA.

## 17 PATIENT COUNSELING INFORMATION

Advise patients to:

- Read the FDA-approved Patient Labeling (Patient Product Information and Instructions for Use).
- Discontinue use of AFSTYLA in case of a hypersensitivity reaction and contact their healthcare provider and/or seek emergency care, depending on the severity of the reaction. Early signs of hypersensitivity reactions may include hives, itching, facial swelling, tightness of the chest, and wheezing *[see Warnings and Precautions (5.1)]*.
- Contact their healthcare provider or hemophilia treatment facility for further treatment and/or assessment if they experience a lack of a clinical response to Factor VIII replacement therapy, as in some cases this may be a manifestation of an inhibitor *[see Warnings and Precautions (5.2)]*.
- Report any adverse reactions or problems following AFSTYLA administration to their healthcare provider.

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for:
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## *FDA-Approved Patient Labeling*

Patient Product Information (PPI)

**AFSTYLA / af stŷ 'lah /**

**Antihemophilic Factor (Recombinant), Single Chain**

**Freeze-Dried Powder for Reconstitution**

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

**What is the most important information I need to know about AFSTYLA?**

- **Your healthcare provider or hemophilia treatment center will instruct you on how to do an infusion on your own.**
- Carefully follow your healthcare provider's instructions regarding the dose and schedule for infusing this medicine.

**What is AFSTYLA?**

- AFSTYLA, Antihemophilic Factor (Recombinant), Single Chain is a medicine used to replace clotting Factor VIII that is missing in patients with hemophilia A.
- Hemophilia A is an inherited bleeding disorder that prevents blood from clotting normally.
- Does not contain human plasma-derived proteins or albumin.
- Your healthcare provider may give you this medicine when you have surgery.
- Is used to treat and control bleeding in all patients with hemophilia A.
- Can reduce the number of bleeding episodes when used regularly (prophylaxis) and reduce the risk of joint damage due to bleeding.
- Is not used to treat von Willebrand disease.

**Who should not use AFSTYLA?**

You should not use AFSTYLA if you:

- Have had a life-threatening allergic reaction to it in the past.
- Are allergic to its ingredients or hamster proteins.

Tell your healthcare provider if you are pregnant or breastfeeding because AFSTYLA may not be right for you.

**What should I tell my healthcare provider before using AFSTYLA?**

Tell your healthcare provider if you:

- Have or have had any medical problems.
- Take any medicines, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies.
- Have any allergies, including allergies to hamster proteins.
- Are pregnant or planning to become pregnant. It is not known if AFSTYLA may harm your unborn baby.
- Are breastfeeding. It is not known if AFSTYLA passes into the milk or if it can harm your baby.
- Have been told you have inhibitors to Factor VIII (because this medicine may not work for you).

**How should I use AFSTYLA?**

- Administered directly into the bloodstream.
- Use as ordered by your healthcare provider.
- You should be trained on how to do intravenous injections by your healthcare provider or hemophilia treatment center. Once trained, many patients with hemophilia A are able to inject this medicine by themselves or with the help of a family member.
- Your healthcare provider will tell you how much to use based on your weight, the severity of your hemophilia A, and where you are bleeding.
- You may need to have blood tests done after getting to be sure that your blood level of Factor VIII is high enough to clot your blood.
- Call your healthcare provider right away if your bleeding does not stop after taking this medicine.

**What are the possible side effects of AFSTYLA?**

- Allergic reactions may occur. Immediately stop treatment and call your healthcare provider right away if you get a rash or hives, itching, tightness of the chest or throat, difficulty breathing, light-headedness, dizziness, nausea, or decrease in blood pressure.
- Your body may form inhibitors to Factor VIII. An inhibitor is a part of the body's defense system. If you form inhibitors, it may stop this medicine from working properly. Your healthcare provider may need to test your blood for inhibitors from time to time.
- Common side effects are dizziness and allergic reactions.
- These are not the only side effects possible. Tell your healthcare provider about any side effect that bothers you or does not go away.

**What are the AFSTYLA dosage strengths?**

AFSTYLA comes in 5 different dosage strengths: 250, 500, 1000, 2000, or 3000 International Units (IU). The actual strength is printed on the carton and vial label.

| Fill Size Color Indicator | Strengths |
|---|---|
| Orange | Dosage strength of approximately 250 IU per vial |
| Blue | Dosage strength of approximately 500 IU per vial |
| Green | Dosage strength of approximately 1000 IU per vial |
| Purple | Dosage strength of approximately 2000 IU per vial |
| Yellow | Dosage strength of approximately 3000 IU per vial |

Always check the actual dosage strength printed on the label to make sure you are using the strength prescribed by your healthcare provider.

**How should I store AFSTYLA?**

- Store this medicine in the original package to protect the vials from light.
- Store this medicine in powder form at 2°C to 8°C (36°F to 46°F). Do not freeze to avoid damage to the diluent vial. It can be stored at room temperature, not to exceed 25°C (77°F), for a single period of up to 3 months, within the expiration date printed on the carton and vial labels.
- If stored at room temperature, record the date that this medicine is removed from refrigeration on the top flap of the carton in the area provided. After storage at room temperature, do not return the product to the refrigerator. The powder form for the product then expires after storage at room temperature for 3 months, or after the expiration date on the product vial, whichever is earlier.
- The reconstituted product (after mixing dry product with diluent) can be stored for 4 hours at a temperature not to exceed 25°C (77°F). Protect from direct sunlight. After reconstitution, if the product is not used within 4 hours, it must be discarded.

**What else should I know about AFSTYLA?**

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

## Instructions for Use of AFSTYLA

**For intravenous use after reconstitution only**

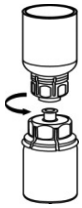
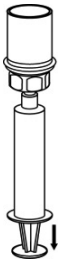
This medicine is infused into a vein. Your healthcare provider or hemophilia treatment center should teach you how to do infusions on your own.

Always follow the specific instructions given by your healthcare provider. The steps listed below are general guidelines for using AFSTYLA. If you are unsure of the instructions, call your healthcare provider before using AFSTYLA. Call your healthcare provider right away if bleeding is not controlled after using AFSTYLA. Your healthcare provider will prescribe the dose that you should take. You may need to take blood tests from time to time. Talk to your healthcare provider before traveling. Dispose of all unused solution, empty vial(s), and other used medical supplies in an appropriate medical waste container.

- **Always work on a clean flat surface** and wash your hands before performing the reconstitution procedures.
- Use only the components for reconstitution that are provided with each package.
- If a package is opened or damaged, do not use and contact your healthcare provider.
- Do not use AFSTYLA beyond the expiration date on the vial and carton labels. If stored at room temperature, the dry product (prior to reconstitution) expires after storage at room temperature for 3 months or after the expiration date on the product vial, whichever is earlier.
- Look at the mixed (reconstituted) solution. Do not use AFSTYLA if the reconstituted solution is cloudy, contains any particles, or is discolored.
- AFSTYLA is for single use only and contains no preservatives. Discard partially used vials.

**AFSTYLA Reconstitution Instructions**

| | | |
|---|---|---|
| 1. | Ensure that the AFSTYLA vial and diluent vial are at room temperature. | |
| 2. | Place the AFSTYLA vial, diluent vial, and Mix2Vial® transfer set on a flat surface. | |
| 3. | Remove AFSTYLA and diluent vial flip caps. Wipe the stoppers with the sterile alcohol swab provided and allow the stoppers to dry prior to opening the Mix2Vial transfer set package. | |
| 4. | Open the Mix2Vial transfer set package by peeling away the lid (Fig. 1). Leave the Mix2Vial transfer set in the clear package. |  Fig. 1 |
| 5. | Place the diluent vial on a flat surface and hold the vial tightly. Grip the Mix2Vial transfer set together with the clear package and push the plastic spike at the blue end of the Mix2Vial transfer set firmly through the center of the stopper of the diluent vial (Fig. 2). |  Fig. 2 |
| 6. | Carefully remove the clear package from the Mix2Vial transfer set. Make sure that you pull up only the clear package, not the Mix2Vial transfer set (Fig. 3). |  Fig. 3 |
| 7. | With the AFSTYLA vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and push the plastic spike of the transparent adapter firmly through the center of the stopper of the AFSTYLA vial (Fig. 4). The diluent will automatically transfer into the AFSTYLA vial. |  Fig. 4 |
| 8. | With the diluent and AFSTYLA vial still attached to the Mix2Vial transfer set, gently swirl the AFSTYLA vial to ensure that the AFSTYLA is fully dissolved (Fig. 5). Do not shake the vial. |  Fig. 5 |

| | | |
|---|---|---|
| 9. | With one hand, grasp the AFSTYLA side of the Mix2Vial transfer set and with the other hand grasp the blue diluent-side of the Mix2Vial transfer set, and unscrew the set into two pieces. (Fig. 6). |  Fig. 6 |
| 10. | Draw air into an empty, sterile syringe. While the AFSTYLA vial is upright, screw the syringe to the Mix2Vial transfer set. Inject air into the AFSTYLA 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). |  Fig. 7 |
| 11. | Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the plunger facing down) and unscrew the syringe from the Mix2Vial transfer set (Fig. 8). |  Fig. 8 |
| 12. | After reconstitution, infuse immediately or within 4 hours. The mixed (reconstituted) solution may be stored at room temperature, not to exceed 25°C (77°F), for up to 4 hours. Do not freeze. Protect from direct sunlight. | |

| | | |
|---|---|---|
| 13. | Record treatment - Remove the peel-off portion of the label from each vial used, and affix it to the patient's treatment diary/log book or scan the vial if recording the infusion electronically. | |
| 14. | If the dose requires more than one vial, use a separate unused Mix2Vial transfer set for each product vial. Repeat step 10 to pool the contents into one syringe. | |

**Administration (intravenous injection)**

- Do not mix AFSTYLA in the same tubing or container with other medicinal products.
- Attach the syringe containing the mixed (reconstituted) solution to a sterile infusion set and give an injection as directed by your healthcare provider or hemophilia treatment center.
- Administer **intravenously. Do not exceed infusion rate of 10 mL per minute.**

**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:**
Customer Support 1-800-683-1288

**For more information, visit www.AFSTYLA.com**

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