PRODUCT MONOGRAPH

HELIXATE® FS

Antihemophilic Factor (Recombinant)

Formulated with Sucrose

IV Injection, 250, 500, 1000, 2000 IU/vial

Coagulation Factor

Distributed by:
Bayer HealthCare LLC
Tarrytown, NY
10591-5097 U.S.A.

Imported into Canada by:
CSL Behring Canada Inc.
55 Metcalfe St., Suite 1460
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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 – Product Information Summary

Route of Administration	Dosage Form, Strength	Clinically Relevant Nonmedicinal Ingredients
intravenous	Lyophilized powder for injection 250, 500, 1000, 2000 IU/vial	Sucrose Glycine Histidine Calcium chloride Sodium Chloride Polysorbate 80 *For a complete listing see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

DESCRIPTION

HELIXATE® FS is a sterile, stable, purified, nonpyrogenic, dried product, which has been manufactured by recombinant DNA technology.

INDICATIONS AND CLINICAL USE

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

When used as a regular prophylactic treatment, HELIXATE® FS is also indicated to prevent the occurrence of spontaneous hemorrhagic episodes and to prevent joint damage in children with no pre-existing joint damage (see Product Monograph Part II: **CLINICAL TRIALS**: **Pediatric Prophylaxis**).

Because HELIXATE® FS showed comparable biological activity to other FVIII preparations, it should be used in the same manner as HELIXATE® (Antihemophilic Factor [Recombinant]). This includes treatment of bleeding in certain patients with inhibitors to FVIII. In clinical studies of HELIXATE®, some patients who developed inhibitors on study continued to manifest a clinical response when inhibitor titres were less than 10 Bethesda Units (B.U.) per mL. When an inhibitor is present, the dosage requirement for FVIII is variable. The dosage can be determined only by clinical response and by monitoring of circulating FVIII levels after treatment (see **DOSAGE AND ADMINISTRATION**).

HELIXATE® FS does not contain von Willebrand Factor and therefore, is not indicated for the treatment of von Willebrand disease.

Geriatrics (>65 years of age)

Clinical studies with HELIXATE® FS did not include sufficient numbers of patients aged 65 and over to be able to determine whether they respond differently from younger patients. However, clinical experience with HELIXATE® and other FVIII products has not identified differences between the elderly and younger patients. As with any patient receiving HELIXATE® FS, dose selection for an elderly patient should be individualized.

Pediatrics (<18 years of age)

HELIXATE® FS is appropriate for use in pediatric patients. Safety and efficacy studies have been performed in two studies (n=60) in less than 4 year old previously untreated and minimally treated pediatric patients.

HELIXATE® FS is comparable to HELIXATE® (Antihemophilic Factor [Recombinant]) in its biological activity and should be used in the same manner as HELIXATE®.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- Known hypersensitivity to mouse or hamster protein.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The development of circulating neutralizing antibodies to FVIII may occur during the treatment of patients with hemophilia A (see **WARNINGS AND PRECAUTIONS**: **Immune**).

General

HELIXATE® FS (Antihemophilic Factor [Recombinant]) is intended for the treatment of bleeding disorders arising from a deficiency in FVIII. This deficiency should be proven prior to administering HELIXATE® FS.

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

Carcinogenesis and Mutagenesis

See Product Monograph PART II: **TOXICOLOGY**: **Carcinogenicity/Mutagenesis** Product Monograph for details.

Immune

The development of circulating neutralizing antibodies to FVIII may occur during the treatment of patients with hemophilia A. Inhibitor formation is especially common in young children with severe hemophilia during their first years of treatment or in patients of any age who have received little previous treatment with FVIII. Nonetheless, inhibitor formation may occur at any time in the treatment of a patient with hemophilia A. Patients treated with any rFVIII preparation, including rFVIII-FS, should be carefully monitored for the development of antibodies to rFVIII by appropriate clinical observation and laboratory tests, according to the recommendation of the patient's hemophilia treatment center. In a clinical study about the use of continuous infusion in surgeries, heparin was used to prevent thrombophlebitis at the infusion site, as with any other long-term intravenous infusions.

Among patients treated with antihemophilic factor products, cases of hypotension, urticaria, and chest tightness in association with hypersensitivity reactions have been reported in the literature. Very rare cases of allergic and anaphylactic reactions have been reported with the predecessor product HELIXATE® (Antihemophilic Factor [Recombinant]), particularly in very young patients or patients who have previously reacted to other FVIII products (see **ADVERSE REACTIONS**: **Post-Market Adverse Drug Reactions**). Serious anaphylactic reactions require immediate emergency treatment with resuscitative measures such as the administration of epinephrine and oxygen.

In clinical studies, HELIXATE® FS has been used in the treatment of bleeding episodes in 37 previously untreated patients (PUPs) and 23 minimally treated pediatric patients ([MTP], defined as having equal to or less than 4 exposure days). Bleeding episodes were treated effectively with 1 or 2 infusions of rFVIII-FS. Overall, 9 out of 60 (15%) patients developed inhibitors. This included 5 out of 37 (14%) PUP and 4 out of 23 (17%) MTP patients treated with HELIXATE ® FS: Overall 6 out of 60 (10%) with a titer above 10 BU and 3 out of 60 (5%) with a titer below 10 BU. The median number of exposure days at the time of inhibitor detection in these patients was 9 days (range: 3 - 18 days) (1, 2).

The median number of exposure days in the clinical studies was 114 (range: 4 – 478). Four of the five patients, who had not achieved 20 exposure days at the end of the study, ultimately achieved more than 20 exposure days in poststudy follow-up and 1 of them developed a low titer inhibitor. The fifth patient was lost to follow-up.

Formation of Antibodies to Mouse and Hamster Protein

Assays to detect seroconversion to mouse and hamster protein were conducted on all patients in clinical studies. None of the patients developed specific antibodies to these proteins following study enrollment and no animal protein associated serious allergic reactions have been observed with rFVIII-FS infusions. Although no such reactions were observed, patients should be made aware of the possibility of a hypersensitivity reaction to mouse and/or hamster protein and alerted to the early signs of such a reaction (eg, hives, localized or generalized urticaria, wheezing and hypotension). Patients should be advised to discontinue use of the product and contact their physician if such symptoms occur.

Special Populations

Pregnant Women

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 whether it affects reproduction capacity. HELIXATE® FS should not be used during pregnancy unless the benefits clearly outweigh any potential risks.

Nursing Women

HELIXATE® FS should not be used during lactation unless the benefits clearly outweigh any potential risks.

Geriatrics (>65 years of age)

Clinical studies with HELIXATE® FS did not include sufficient numbers of patients aged 65 and over to be able to determine whether they respond differently from younger patients. However, clinical experience with HELIXATE® and other FVIII products has not identified differences between the elderly and younger patients. As with any patient receiving HELIXATE® FS, dose selection for an elderly patient should be individualized.

Pediatrics (<18 years of age)

HELIXATE® FS is appropriate for use in pediatric patients. Safety and efficacy studies have been performed in two studies (n=60) in less than 4 year old previously untreated and minimally treated pediatric patients.

HELIXATE® FS is comparable to HELIXATE® (Antihemophilic Factor [Recombinant]) in its biological activity and should be used in the same manner as HELIXATE®.

Monitoring and Laboratory Tests

The clinical effect of HELIXATE® FS is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more HELIXATE® FS than would be estimated in order to attain satisfactory clinical results. If the calculated dose fails to attain the expected FVIII levels or if bleeding is not controlled after administration of the calculated dosage, the presence of a circulating inhibitor in the patient should be suspected. Its presence should be substantiated and the inhibitor level quantitated by appropriate laboratory tests. When an inhibitor is present, the dosage requirement for rFVIII-FS is extremely variable and the dosage can be determined only by the clinical response.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

During the clinical studies conducted in previously treated patients, 109 adverse events were reported out of a total 73 patients infused. Only 13 events were considered to be at least remotely related to rFVIII-FS administration; the relationship of another 7 events to rFVIII-FS administration was non-assessable. Thus, 20 events in 11 patients were considered to be either non-assessable or at least remotely related to rFVIII-FS administration for an incidence of 0.5% relative to the number of infusions administered. Events which were at least remotely drug-related included local site reactions (2), dizziness (2), rash (2), unusual taste in the mouth (2), increased blood pressure (1), pruritus (1), depersonalization/"feeling funny" (1), nausea (1) and rhinitis (1). In clinical studies with 73 previously-treated patients ([PTP], defined as having more than 100 exposure days) followed over four years, no de novo inhibitors were observed.

In clinical studies with previously untreated patients (PUPs) and minimally treated (MTP) pediatric patients, 18 adverse events were reported by the clinical investigators as at least possibly related to the study drug including the expected complication of inhibitor development in 8 patients (included in the 9 patients above), a forearm bleed following venipuncture, constipation, adenopathy, rash, anemia and pallor in one inhibitor patient with gastroenteritis, and serous otitis media.

Table 2 – Adverse Drug Reactions

Blood and lymphatic system disorders	Factor VIII inhibition
Gastrointestinal disorders	Dysgeusia
	Nausea
General disorders and administration site conditions	Injection site reaction
Immune System disorders	Allergic/anaphylactic reaction
Investigations	Blood pressure abnormal
Nervous system disorders	Dizziness
Skin and subcutaneous tissue disorders	Rash
	Pruritis

Post-Market Adverse Drug Reactions

The following events are principally derived from post-marketing experience and publications and accurate rate estimates are generally not possible. Among patients treated with its predecessor product HELIXATE® (Antihemophilic Factor [Recombinant]), very rare cases of serious allergic reactions and anaphylactic reactions have been reported, particularly in very young patients or patients who have previously reacted to other FVIII products. Individual cases of hypotension have been very rarely reported. Rare cases of urticaria have also been reported. Although such serious reactions have not been reported with the use of HELIXATE® FS, it is likely that these may also occur. Rare cases of dyspnea have been reported with HELIXATE® FS.

In extensive postregistration studies with HELIXATE ® FS involving more than 1000 patients, the following was observed: Less than 0.2% PTPs developed de novo inhibitors. In a subset defined as having less than 20 exposure days at study entry, less than 11% developed de novo inhibitors.

DRUG INTERACTIONS

Drug-Drug Interactions

HELIXATE® FS is a recombinant version of FVIII, a physiological human protein. Besides the known interactions of FVIII with other coagulation proteins, no other interactions with other drugs have been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal preparations have not been established.

Drug-Laboratory Interactions

There are no known laboratory interactions.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Each bottle of HELIXATE® FS (Antihemophilic Factor [Recombinant]) has the rFVIII-FS potency in international units stated on the label based on the one-stage assay methodology. The reconstituted product must be administered intravenously by direct syringe injection. The product must be administered within 3 hours after reconstitution. It is recommended to use a microbore tubing administration set to minimize losses of product due to adsorption and volume

retention. HELIXATE® FS should not be mixed with other medicinal products or infusion solutions.

Recommended Dose and Dosage Adjustment

The dosages described below are presented as general guidance. It should be emphasized that the dosage of HELIXATE® FS required for hemostasis must be individualized according to the needs of the patient, the severity of the deficiency, the severity of the hemorrhage, the presence of inhibitors and the FVIII level desired. It is often critical to follow the course of therapy with FVIII level assays.

The clinical effect of HELIXATE® FS is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more HELIXATE® FS than would be estimated in order to attain satisfactory clinical results.

It has been shown in a clinical study performed in 14 adults with severe hemophilia A (≤1% FVIII:C) undergoing a major surgery that HELIXATE ® FS can be used for continuous infusion in surgeries (pre- and postoperative). In this study, heparin was used to prevent thrombophlebitis at the infusion site, as with any other long-term intravenous infusions. For the calculation of the initial infusion rate, clearance can be obtained by performing a presurgery decay curve, or by starting from an average population value (3.0-3.5 mL/h/kg) and then adjusting accordingly.

Infusion rate (in IU/kg/h) = Clearance (in mL/h/kg) x desired factor VIII level (in IU/mL)

Continuous infusion, clinical, and in vitro stability has been demonstrated using ambulatory pumps with a polyvinyl chloride (PVC) reservoir. HELIXATE® FS contains low levels of polysorbate-80 as an excipient, which is known to increase the rate of di-(2-ethylhexyl)phthalate (DEHP) extraction from PVC materials. This should be considered for a continuous infusion administration (see **Reconstitution**: **For Continuous Infusion**).

If the calculated dose fails to attain the expected FVIII levels or if bleeding is not controlled after administration of the calculated dosage, the presence of a circulating inhibitor in the patient should be suspected. Its presence should be substantiated and the inhibitor level quantitated by appropriate laboratory tests. When an inhibitor is present, the dosage requirement for rFVIII-FS is extremely variable and the dosage can be determined only by the clinical response.

Some patients with low titre inhibitors (<10 B.U.) can be successfully treated with rFVIII-FS without a resultant anamnestic rise in inhibitor titre. Factor VIII levels and clinical response to treatment must be assessed to ensure adequate response. Use of alternative treatment products, such as Factor IX Complex products, Antihemophilic Factor (Porcine), recombinant Factor VIIa or Anti-Inhibitor Coagulant Complex may be necessary for patients with anamnestic responses to FVIII treatment and/or high titre inhibitors.

Calculation of Dosage

The in vivo percent increase in FVIII level can be estimated by multiplying the dose of rFVIII-FS per kilogram of body weight (IU/kg) by 2%. This method of calculation is based on clinical findings by Abildgaard et al. (3) and is illustrated in the following examples.

Equation 1 – Calculation of HELIXATE® FS Dosage (Expected % FVIII Increase)

$$\text{Expected \% FVIII increase} = \frac{(\#\ \text{units administered}) \times 2\%/\text{IU/kg}}{\text{body weight (kg)}}$$

$$\text{Example for a 70 kg adult}: \frac{1400\ \text{IU} \times 2\%/\text{IU/kg}}{70\ \text{kg}} = 40\%$$

Equation 2 – Calculation of HELIXATE® FS Dosage (Dosage Required)

$$\text{Dosage required (IU)} = \frac{(\text{body weight (kg)}) \times (\text{desired \% FVIII increase})}{2\%/\text{IU/kg}}$$

$$\text{Example for a 15 kg child}: \frac{15\ \text{kg} \times 100\%}{2\%/\text{IU/kg}} = 750\ \text{IU required}$$

The dosage necessary to achieve hemostasis depends upon the type and severity of the bleeding episode, according to the following general guidelines.

Table 3 – Dosage Necessary to Achieve Hemostasis

Hemorrhagic Event	Therapeutically Necessary Plasma Level of FVIII Activity	Dosage Necessary to Maintain the Therapeutic Plasma Level
Minor Hemorrhage (superficial, early hemorrhages, hemorrhages into joints)	20-40%	10- 20 IU per kg Repeat dose if evidence of further bleeding.
Moderate to Major Hemorrhage (3) (hemorrhages into muscles, hemorrhages into the oral cavity, definite hemarthroses, known trauma)	30-60%	15-30 IU per kg Repeat one dose at 12-24 hours if needed.
Surgery (minor surgical procedures)		

Table 3 – Dosage Necessary to Achieve Hemostasis

Hemorrhagic Event	Therapeutically Necessary Plasma Level of FVIII Activity	Dosage Necessary to Maintain the Therapeutic Plasma Level
Major to Life-Threatening Hemorrhage (intracranial, intra-abdominal or intra thoracic hemorrhages, gastrointestinal bleeding, central nervous system bleeding, bleeding in the retro pharyngeal or retro peritoneal spaces or iliopsoas sheath)	80-100%	Initial dose 40-50 IU per kg Repeat dose 20-25 IU per kg every 8-12 hours.
Fractures		
Head Trauma		
Surgery (major surgical procedures)	~100%	a) By bolus infusions Preoperative dose 50 IU/kg Verify ~100% activity prior to surgery. Repeat as necessary after 6 to 12 hours initially and for 10 to 14 days until healing is complete. b) By continuous infusion Raise factor VIII activity presurgery with an initial bolus infusion and immediately follow with continuous infusion (in IU/h/kg) adjusting according to patient's daily clearance and desired factor VIII levels for at least 7 days.

Prophylaxis

FVIII products may also be administered on a regular schedule for prophylaxis of bleeding, as reported by Nilsson et al. (4, 5). In children, the recommended dose for a regular prophylaxis schedule is 25 IU/kg of body weight every other day (6).

Immune Tolerance

FVIII products have been administered to patients on a high dose schedule in order to induce immune tolerance to FVIII, which resulted in disappearance of the inhibitor activity. There is currently no consensus among treaters to the optimal treatment schedule.

Administration

For details on precautions associated with administration, see **WARNINGS AND PRECAUTIONS**: **General**.

Rate of Administration

The rate of administration should be adapted to the response of the individual patient but administration of the entire dose in 5 to 10 minutes or less is well-tolerated.

HELIXATE® FS can be infused by continuous infusion. The infusion rate should be calculated based on the clearance and the desired FVIII level. In a clinical study performed in 14 adults with severe hemophilia A (≤1% FVIII:C) who underwent a major surgery, the range of infusion rates for HELIXATE ® FS was 0.2 to 3.6 mL/h. Example: For a 75 kg patient with a clearance of 3 mL/h/kg, the initial infusion rate would be 3 IU/h/kg to achieve a FVIII level of 100%. For calculation of mL/h, multiply infusion rate in IU/h/kg by kg bw/concentration of solution (IU/mL).

Table 4 – Calculation of Infusion Rate Based on Clearance and the Desired FVIII Level

	Desired Plasma FVIII Level	**Infusion Rate (IU/h/kg)**	**Infusion Rate for 75 kg Patient, mL/h**		
Clearance : 3 mL/h/kg			**Concentrations of rFVIII Solution**		
			100 IU/mL	**200 IU/mL**	**400 IU/mL**
	100% (1 IU/mL)	3.0	2.25	1.125	0.56
	60% (0.6 IU/mL)	1.8	1.35	0.68	0.34
	40% (0.4 IU/mL)	1.2	0.9	0.45	0.225

Higher infusion rates may be required in conditions with accelerated clearance during major bleeds and extensive tissue damage during surgical interventions. Subsequent infusion rates should be calculated based on the actual FVIII levels and recalculated clearance for each day post surgery based on the equation: clearance = infusion rate/actual FVIII level.

Reconstitution

Parenteral Products

HELIXATE® FS powder should only be reconstituted with the supplied diluent (2.5 or 5.0 mL Sterile Water for Injection) using the supplied sterile transfer device. Reconstitution and dilution should be performed in accordance with good practices rules, particularly with attention to asepsis. Always work on a clean surface and wash your hands before performing the following procedures.

1. Warm the unopened diluent and the product to room temperature (no more than 37°C).
2. Place the product vial, diluent vial and Mix2Vial™ on a flat surface.
3. Ensure product and diluent vial flip caps are removed and the stoppers are treated with an aseptic solution and allowed to dry prior to opening the Mix2Vial package.
4. Open the Mix2Vial package by peeling away the lid (Fig. 1). Leave the Mix2Vial in the clear package. Place the diluent vial on an even surface and hold the vial tight. Grip the

Mix2Vial together with the package and snap the blue end onto the diluent stopper (Fig. 2).

5. Carefully remove the clear package from the Mix2Vial set. Make sure that you only pull up the package and not the Mix2Vial set (Fig. 3).
6. With the product vial firmly on a surface, invert the diluent vial with the set attached and snap the transparent adapter onto the product vial stopper (Fig. 4). The diluent will automatically transfer into the product vial.
7. With the diluent and product vial still attached, gently swirl the product vial to ensure the product is fully dissolved (Fig. 5). Do not shake vial.
8. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the blue diluent-side of the Mix2Vial set and unscrew the set into two pieces (Fig. 6).
9. Draw air into an empty, sterile syringe. While the product vial is upright, screw the syringe to the Mix2Vial set. Inject air into the product vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly (Fig. 7).
10. Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the syringe plunger facing down) and unscrew the syringe from the Mix2Vial set (Fig. 8).

For Bolus Injection

11. Attach the syringe to an administration set made with microbore tubing. Use of administration sets without microbore tubing may result in a larger retention of the solution within the administration set.
12. If the same patient is to receive more than one bottle, the contents of two bottles may be drawn into the same syringe through a separate unused Mix2Vial set before attaching the vein needle.
13. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Figure 1 – Reconstitution Procedure

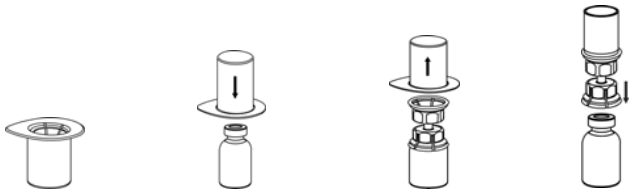

Fig. 1 Fig. 2 Fig. 3 Fig. 4

Figure 1 – Reconstitution Procedure

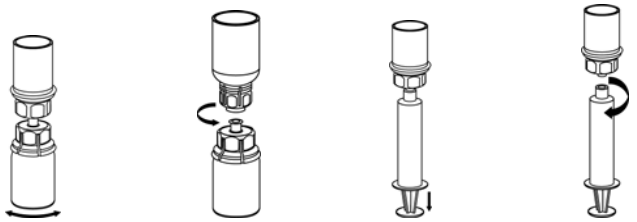

Fig. 5 Fig. 6 Fig. 7 Fig. 8

Table 5 – Reconstitution of Parenteral Products

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
250 IU	2.5 mL	2.5 mL	100 IU/ mL
500 IU	2.5 mL	2.5 mL	200 IU/mL
1000 IU	2.5 mL	2.5 mL	400 IU/mL
2000 IU	5.0 mL	5.0 mL	400 IU/mL

For Continuous Infusion

Reconstitute HELIXATE® FS according to Steps 1-10 above. Continuous infusion of HELIXATE® FS must employ an infusion pump that can provide continuous delivery, deal with low volumes and low infusion speeds. Technical instructions of the pump manufacturer, including the devices to be used, should be followed. The reservoir of the pump should be filled under aseptic conditions and the reservoir and tubing should be changed at least every 24 hours. In a clinical study performed in 14 adults with severe hemophilia A (≤1%FVIII:C) undergoing a major surgery, a minute amount of heparin was added to the infusion solution (final concentration of 5 U/mL) in order to prevent local thrombophlebitis at the site of the infusion. Refer to Table 4 for infusion rates.

Note: HELIXATE® FS reconstituted with 2.5 mL or 5.0 mL Sterile Water for Injection should not be further diluted

OVERDOSAGE

No symptoms of overdose have been reported.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

See **INDICATIONS AND CLINICAL USE**.

Pharmacodynamics

The activated partial thromboplastin time (aPTT) shortened appropriately with both HELIXATE® (Antihemophilic Factor [Recombinant]) (rFVIII) and rFVIII-FS.

Pharmacokinetics

Initial pharmacokinetic studies were conducted in 35 patients, with severe hemophilia A (7).

Absorption

Not applicable. HELIXATE® FS is administered directly into the blood stream by IV injection.

Distribution

No specific distribution studies have been performed, however after administration of HELIXATE® FS (Antihemophilic Factor [Recombinant]), peak factor VIII activity decreases by a two-phase exponential decay. This is similar to that of plasma-derived factor VIII. HELIXATE® FS binds to its natural protein carrier vWF and is mostly confined into the vascular space.

Metabolism

HELIXATE® FS is metabolized as it produces its biological activity during the activation of the coagulation cascade.

Excretion

After administration of HELIXATE® FS (Antihemophilic Factor [Recombinant]), peak factor VIII activity decreased by a two-phase exponential decay with a mean terminal half-life of about 15 hours. This is similar to that of plasma-derived factor VIII which has a mean terminal half-life of approximately 13 hours. The half-life data for rFVIII-FS were unchanged after 24 weeks of exclusive treatment, indicating continued efficacy and no evidence of FVIII inhibition.

Duration of Effect

The duration of effect is variable and dependent on the individual patient, the severity of the bleed and the clinical situation.

STORAGE AND STABILITY

HELIXATE® FS (Antihemophilic Factor [Recombinant]) should be stored under refrigeration (2-8°C). Storage of lyophilized powder at room temperature (up to 25°C) for 3 months, such as in home storage situations, may be done. If the product is stored outside the refrigerator, please add the date removed from refrigeration and note a new expiry date on the carton and vial. The new expiry date should be 3 months from the date product is removed from the refrigerator, or the previously stamped expiry date, whichever is shorter. Once product is removed from refrigeration, it cannot be returned to the refrigerator. Freezing must be avoided. Protect from extreme exposure to light and store the lyophilized powder in the carton prior to use.

After reconstitution, the product should be used immediately. For continuous infusion, stability has been demonstrated for 48 hours at 30°C.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

Table 6 – HELIXATE® FS Vial Sizes

Approximate Factor VIII Activity	Dosage	Diluent
250 IU	L-Low	2.5 mL
500 IU	M-Mid	2.5 mL
1000 IU	H-High	2.5 mL
2000 IU	U - Ultra-High	5 mL

Each vial of HELIXATE® FS contains the labelled amount of rFVIII in international units (IU). One IU, as defined by the World Health Organization standard for blood coagulation FVIII, human, is approximately equal to the level of FVIII activity found in 1 mL of fresh pooled human plasma. The final product, when reconstituted as directed, contains the following ingredients.

Table 7 – HELIXATE® FS Inactive Ingredients

Inactive Ingredient/Excipient	250 IU, 500 IU, 1000 IU Vial Size	2000 IU Vial Size
Sucrose	0.9-1.3%	0.9-1.2%
Glycine	21-25 mg/mL	20-24 mg/mL
Histidine	18-23 mM	17-22 mM
Calcium Chloride ($CaCl_2$)	2-3 mM	1.9-2.9 mM
Sodium	27-36 mEq/L	26-34 mEq/L
Chloride	32-40 mEq/L	31-38 mEq/L
Polysorbate 80	64-96 µg/mL	64-96 µg/mL

The product contains no preservative. HELIXATE® FS must be administered by the intravenous route.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	HELIXATE® FS
Common name:	Antihemophilic Factor [Recombinant]

Product Characteristics

HELIXATE® FS is produced by Baby Hamster Kidney (BHK) cells into which the human factor VIII (FVIII) gene has been introduced. The BHK cell culture medium, which is used during manufacturing contains Human Plasma Protein Solution (HPPS) and recombinant insulin, but does not contain any proteins derived from animal sources. HELIXATE® FS incorporates a revised purification process and eliminates the addition of Albumin (Human) in the formulation of the final preparation.

HELIXATE® FS is a highly purified glycoprotein consisting of multiple peptides including an 80 kD and various extensions of the 90 kD subunit.

Studies to further elucidate the carbohydrate structure of rFVIII, indicated that both pdFVIII and rFVIII contain mainly high mannose type and complex-type sugar chains.

Viral Inactivation

The purification process includes an effective 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 FVIII (rFVIII) and remove contaminating substances.

Prion Inactivation

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 variant Creutzfeldt-Jakob Disease (vCJD) and Creutzfeldt-Jakob Disease (CJD) agents. Several of the individual production and raw material preparation steps in the HELIXATE® FS manufacturing process have been shown to decrease TSE infectivity of that experimental model agent. TSE reduction steps included the Fraction II+III separation step for Human Plasma Protein Solution (6.0 $\log_{10}$) and an anion exchange chromatography step for the HELIXATE® FS process (3.6 $\log_{10}$). These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

CLINICAL TRIALS

Study demographics and trial design

A total of 73 patients with severe hemophilia A, age 12-59, who had been previously treated with other recombinant/plasma-derived FVIII products were enrolled in two 6-month studies of home therapy with rFVIII-FS, one in Europe and one in North America. A total of 3960 infusions (or 7.03 million units) of rFVIII-FS were administered during this portion of the studies. Treatment of 659 bleeding episodes during the study period required 951 infusions of rFVIII-FS. A significant number (92.7%) of bleeding episodes were treated successfully with one or two infusions, with a median dosage of 27.3 IU/kg per treatment infusion. Prophylactic treatment accounted for 64% of infusions administered during the studies. Nine patients have received rFVIII-FS on 11 occasions for surgical procedures. The procedures included removal of a brain tumour, two total knee replacements, two joint synovectomies (one with Achilles tendon lengthening), two circumcisions, a hernia repair and three teeth extractions. Hemostasis was satisfactory in all cases (1, 7, 8).

For additional details, see Product Monograph Part I: **ACTION AND CLINICAL PHARMACOLOGY**.

Study results

These two six-month studies showed that HELIXATE® FS demonstrates comparable efficacy to HELIXATE®. Treatment with HELIXATE® FS was associated with an excellent efficacy profile when used in the treatment of patients with hemophilia A.

Pediatric Prophylaxis

Sixty-five young boys less than 30 months of age with severe hemophilia A (factor VIII level ≤ 2 IU/dL) and normal joints, as well as a history of less than 3 hemorrhages in the same joints, were observed for 5 years in a multicenter, open-label, prospective, randomized, controlled clinical study (6). Patients received either 25 IU/kg every other day (prophylaxis; n=32) or at least 3 doses totaling a minimum of 80 IU/kg at the time of a bleeding episode (enhanced episodic; n=33). Endpoints were joint damage evaluated by magnetic resonance imaging (MRI) and/or radiography, as well as the frequency of bleeding episodes (joint bleeds and other bleeds). Joint damage detected by MRI or x-ray in the ankles, knees, and elbows (ie, 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 higher risk of experiencing 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 (P<0.001). Three subjects (9%) receiving episodic treatment experienced recurrent life-threatening hemorrhages versus no subjects receiving prophylactic treatment (P=0.238). Three patients in the prophylaxis group developed high-titer inhibitors compared to none in the enhanced episodic group. While many of the detected inhibitors were low titer and transient, the overall incidence

of inhibitor development in PUPs and MTPs was 13% across both study groups, which is comparable to a demonstrated incidence of 15% in a previous randomized controlled trial (1).

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacologic activity of rFVIII-FS has been demonstrated *in vitro* in both clotting and factor Xa assays. Binding to von Willebrand Factor has also been demonstrated. The genetic, biochemical and clinical demonstration of FVIII deficiency in a colony of miniature Schnauzer dogs has been reported. As well, the efficacy of rFVIII in this animal model has been proven.

In a study of rFVIII-FS, two dogs previously untreated with FVIII were administered rFVIII-FS and two dogs previously treated with FVIII were administered rFVIII. Each preparation was infused at approximately 400 IU/kg. Animals treated with rFVIII-FS displayed a correction of bleeding time, as well as normalization of biochemical parameters of bleeding. FVIII recovery, as determined by immunoreactivity, appeared similar in all treated animals.

Animals in the safety pharmacology studies received doses of 300 IU/kg, representing a significant margin of safety when compared to the intended therapeutic dosage (25 IU/kg). The most significant effect noted was a transient increase in arterial pressure in rats, related to the relative amount of glycine in the 250 IU compared to the 500 and 1000 IU fill sizes. This is a species-specific effect observed with other proteins that use glycine as an excipient and does not present a risk to the human population.

A common test-article related finding in rabbits was a decrease in the aPTT, a measure of the activated clotting time of blood. This was not unexpected in that FVIII is required for activity. Since all animals received the same dose of material (300 IU/kg), no conclusions with regard to dose/response relationship between the aPTT and test article can be made.

In conclusion, there does not appear to be any untoward effects of rFVIII-FS on the organ systems evaluated.

In five separate infusion studies in rabbits, rFVIII-FS displayed similar pharmacokinetics to that of rFVIII. The molecule behaved similarly from experiment to experiment. There was interstudy variance with the area under the curve and clearance in one study, displaying slightly lower and higher values, respectively, versus all other studies. This is most likely the result of metabolic differences in the rabbits used in each study. Overall, the degree of homology between studies is quite remarkable.

Human Pharmacology

The activated partial thromboplastin time (aPTT) shortened appropriately with both HELIXATE® (Antihemophilic Factor [Recombinant]) (rFVIII) and rFVIII-FS.

Absorption and Bioavailability

HELIXATE® FS is administered by IV injection and the whole dose is available in the bloodstream. The recovery data for rFVIII-FS were unchanged after 24 weeks of exclusive treatment, indicating continued efficacy and no evidence of FVIII inhibition. The mean FVIII recovery measured 10 minutes following a dose of rFVIII-FS in 73 patients after 24 weeks of treatment with rFVIII-FS was 2%/IU/kg, which was unchanged from FVIII recovery determined at baseline and at Weeks 4 and 12.

Pharmacokinetics

Initial pharmacokinetic studies were conducted in 35 patients, with severe hemophilia A.

Distribution

No specific distribution studies have been performed, however after administration of HELIXATE® FS (Antihemophilic Factor [Recombinant]), peak factor VIII activity decreases by a two-phase exponential decay. This is similar to that of plasma-derived factor VIII. HELIXATE® FS binds to its natural protein carrier vWF and is mostly confined into the vascular space.

Metabolism

No specific metabolism studies have been performed. HELIXATE® FS as regular FVIII is metabolized as it produces its biological activity during the activation of the coagulation cascade.

Excretion

After administration of HELIXATE® FS (Antihemophilic Factor [Recombinant]), peak factor VIII activity decreased by a two-phase exponential decay with a mean terminal half-life of about 15 hours. This is similar to that of plasma-derived factor VIII which has a mean terminal half-life of approximately 13 hours. The half-life data for rFVIII-FS were unchanged after 24 weeks of exclusive treatment, indicating continued efficacy and no evidence of FVIII inhibition.

Mean baseline clearance for 14 adult patients undergoing major surgeries with continuous infusion is 188 mL/h corresponding to 3.0 mL/h/kg (range 1.6-4.6 mL/h/kg).

TOXICOLOGY

Acute Toxicity

The acute intravenous toxicity of rFVIII-FS was determined in mice, rats and rabbits. The intravenous LD_{50}'s are >50, >33 and >10 mL/kg, respectively. Only rats failed to tolerate the planned dose (135 mL/kg) and this was most likely due to a species related sensitivity to the excipient, glycine. Nevertheless, with the high doses tolerated, a wide margin of safety has been shown with the doses administered in these three species.

Gal α 1-3Gal Structure in rFVIII

Studies to further elucidate the carbohydrate structure of rFVIII, indicated that both pdFVIII and rFVIII contain mainly high mannose type and complex-type sugar chains. While some overall quantitative configuration differences were observed, these were not regarded as significant: however, these investigations did reveal the presence of a unique terminal sugar structure in a minority of the rFVIII molecules, a galactose α 1-3 galactosyl (gal α 1-3 gal) group.

Biological Significance of Gal α-3

Literature reports indicate the potential for interaction of naturally occurring anti-α gal antibody with rFVIII bearing this structure. This may result in altered pharmacokinetics, reduced clinical efficacy or acute intolerance to rFVIII containing this structure. A series of preclinical experiments were conducted to address these issues.

Baboons were infused with either plasma-derived FVIII or an experimental batch of rFVIII with α gal content in the range of 5M/M FVIII (ie, approximately 10-fold greater than the amount in clinical lots of rFVIII). All preparations were labelled with radioactive iodine to facilitate monitoring. The results of these studies indicated little if any difference between the two preparations, suggesting that in this model the presence of this carbohydrate structure was of minimal (if any) biological significance. No anomalous tissue distribution or excretion of the α gal-containing rFVIII was observed.

In an effort to assess actual recovery effects of this structure, baboons were infused with large doses (300 IU/kg) of the preparations or a clinical lot of rFVIII and actual FVIII:C levels monitored over a 60 minute interval; no significant consistent difference in increment in FVIII:C titres was observed. Importantly, despite the 10-fold greater content of α gal residue in the experimental lot and the demonstration of substantial anti-α antibody titres in all animals, no acute intolerance (ie, anaphylaxis) was observed in these studies nor were any physiological or biochemical anomalies recorded over several weeks of observation. It can be concluded from these studies that the presence of this structure in rFVIII does not appear to confer any acute tolerance problems.

In conclusion, no apparent clinically or biologically significant consequence to the presence of the gal α 1-3 gal carbohydrate structure in rFVIII has been demonstrated despite evidence of circulating antibody capable of recognizing this residue in appropriate animal species. While in vitro systems clearly indicate anti-α gal antibody found in humans can bind to rFVIII bearing these structures, extrapolation to in vivo effects does not appear possible. This may be due to the relatively low concentration of this structure in clinical lots of rFVIII, the association of FVIII with von Willebrand Factor in circulation or other as yet unexplored reasons. Results from our studies have permitted a conclusion that this carbohydrate structure confers little if any significant consequence to the biological fate of rFVIII.

Repeated Dose Toxicity

Repeated administration studies were performed in two species: rabbits and dogs. The animals were administered 305 IU/kg of rFVIII-FS intravenously on five successive days to assess the

effects of repeated administration. One group of animals was sacrificed on the day following the fifth infusion (Day 6), another was sacrificed four weeks (Day 33) after the series of infusions in order to assess delayed effects.

No adverse effects were seen in rabbits with regard to weight gain, hematology, blood chemistry or necropsy. Five of the 24 rabbits showed an antibody titre prior to dosing or on Day 6 following administration of rFVIII-FS or the excipient control substance. Four of the 6 rabbits in the rFVIII-FS Day 33 group mounted an antibody titre to rFVIII-FS by Day 33. There were no apparent adverse effects in those rabbits that developed a titre. Histopathology evaluation did not reveal any treatment-related changes and no immune-mediated pathology was seen.

No adverse effects were seen in dogs with regard to urinalysis, necropsy, or histopathology. Statistically significant changes in hematology and blood chemistry (both between and within groups) were observed; however, these changes were slight and not considered to be of clinical significance. Antibodies were not detected at Day 6. Three of the 4 dogs administered rFVIII-FS, as well as one dog inadvertently administered rFVIII-FS on the third day of infusion, developed an antibody titre at Day 33. No adverse effects were seen in dogs that developed an antibody titre.

Results of the acute and repeated dose studies indicate a low order of toxicity for rFVIII-FS, except for apparent immunological responses to the heterologous protein. The antibody response is not expected in the clinic. With the expected clinical dose of 25 IU/kg, a wide margin of safety of rFVIII-FS has been demonstrated in laboratory animals.

Neoantigenicity

Theoretically, the process of protein purification has the potential to induce changes in the molecule that may induce an immune response when administered. In preclinical models, many therapeutic proteins have been shown to induce an antibody response with repeated administration. In order to determine if the solvent/detergent purification process induces physical or conformation changes that produce new epitopes on the rFVIII model, four neoantigenicity studies using alternate protein: excipient ratios of rFVIII-FS and “high aggregate” lots, were performed that make use of the naturally occurring immune response to foreign proteins. The methodology involved hyperimmunization of rabbits with rFVIII-FS. Serum containing antibodies to the rFVIII-FS was tested for unique epitopes compared to rFVIII. In each study, all antibodies cross-reacted with both rFVIII and rFVIII-FS.

Carcinogenicity/Mutagenesis

In vitro evaluation of the mutagenic potential of rFVIII failed to demonstrate reverse mutation or chromosomal aberrations at doses substantially greater than the maximum expected clinical dose. In vivo evaluation of rFVIII in animals using doses ranging between 10 and 40 times the expected clinical maximum also indicated that rFVIII does not possess a mutagenic potential. Long-term investigations of carcinogenic potential in animals have not been performed.

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PART III: CONSUMER INFORMATION

HELIXATE® FS

Antihemophilic Factor (Recombinant)

Formulated with Sucrose

This leaflet is Part 3 of a three-part "Product Monograph" published when HELIXATE® FS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about HELIXATE® FS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

HELIXATE® FS (Antihemophilic Factor [Recombinant]) is used for the treatment of hemophilia A. Patients who have hemophilia A do not have enough clotting Factor VIII, which helps control bleeding. HELIXATE® FS can be used to prevent bleeding before it happens, or it can be used to stop a bleeding episode that has already begun in patients who have hemophilia A.

What it does:

HELIXATE® FS is clotting Factor VIII that has been developed in the laboratory. It is very similar to the Factor VIII that occurs naturally in human blood. In patients with hemophilia A, who do not have enough natural Factor VIII in their blood, HELIXATE® FS gives them additional Factor VIII to help prevent and/or control bleeding. HELIXATE® FS is given directly into the blood through an injection in a vein.

When used as a regular prophylactic treatment, HELIXATE® FS is also indicated to prevent the occurrence of spontaneous hemorrhagic episodes and to prevent joint damage in children.

When it should not be used:

HELIXATE® FS does not contain von Willebrand Factor and therefore, is not indicated for the treatment of von Willebrand disease.

What the medicinal ingredient is:

Antihemophilic Factor (Recombinant)

What the nonmedicinal ingredients are:

- Sucrose
- Glycine
- Histidine
- Calcium chloride
- Sodium
- Chloride
- Polysorbate 80

HELIXATE® FS does not contain any preservatives.

What dosage forms it comes in:

HELIXATE® FS is a dried product powder available in vials containing 250 IU*, 500 IU, 1000 IU, (with 2.5 mL Sterile Water for Injection), and 2000 IU (with 5.0 mL Sterile Water for Injection) supplied with a Mix2Vial™ filter transfer set. After reconstitution, HELIXATE® FS is given by direct injection into a vein, usually over 5 to 10 minutes. You may also receive treatment presurgery by an initial bolus (all at once) injection followed immediately by continuous infusion.

* IU = International Units

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Some people can develop *inhibitors* to treatment with Factor VIII.

Inhibitors to treatment with Factor VIII are antibodies that can reduce the effectiveness of treatment. Anyone can develop inhibitors, but they are especially common in young children with severe hemophilia during their first years of treatment and any patient who has had little previous treatment with Factor VIII. Your hemophilia healthcare team will monitor you carefully for the development of inhibitors.

Be careful when handling the administration set and needle, to minimize the possibility of accidental needlestick injuries. Contact your healthcare team immediately if you accidentally injure yourself.

Rarely, some people have allergic reactions to Factor VIII. If you develop low blood pressure, a rash, hives, wheezing, or tightness in your chest, seek immediate emergency treatment.

BEFORE you use HELIXATE® FS talk to your doctor or pharmacist if

- you are allergic to mouse or hamster protein, or any of the ingredients in HELIXATE® FS.
- you have had inhibitor development in the past.

you are pregnant, are trying to become pregnant or are a nursing mother.

INTERACTIONS WITH THIS MEDICATION

None known.

See also ABOUT THIS MEDICATION: When it should not be used, and SIDE EFFECTS AND WHAT TO DO ABOUT THEM.

PROPER USE OF THIS MEDICATION

Usual dose

Your doctor will calculate the best dosage for you, based on your weight, blood tests of your Factor VIII level, and whether HELIXATE® FS is being used to prevent or stop a bleeding episode. You and your healthcare team will work together to find out what dosage and schedule works best for you.

General guidelines for dosage:

- A minor bleeding episode will be treated with 10-20 IU for every kilogram of body weight.
- A moderate/major bleeding episode will be treated with 15-30 IU for every kilogram of body weight.
- A major/very serious bleeding episode will be treated with 40-50 IU for every kilogram of body weight.
- Surgical procedures may require 50 IU for every kilogram of body weight before the operation. You may also receive treatment presurgery by an initial bolus (all at once) injection followed immediately by continuous infusion.
- Patients who have inhibitors may require higher dosages.
- The regular prophylaxis schedule for children is 25 IU/kg of body weight every other day.

Overdose

No symptoms of overdose have been reported.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In patients who have had previous treatment with Factor VIII, the number of side effects were very low. Some side effects included reactions at the injection site, dizziness, rash, unusual taste in the mouth, increased blood pressure, itchy skin, depersonalization/"feeling funny", nausea, and runny nose.

In patients who had no previous treatment with Factor VIII, some side effects included bleeding after the injection, constipation, swollen glands, rash, anemia, and ear infection.

You may find that more HELIXATE® FS is required than estimated to stop the bleeding (lack of effect).

If you are concerned about any possible side effects, talk to your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/ Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Common			
Lack of Effect		✓	
Uncommon			
Allergic Reaction: low blood pressure, rash, hives, wheezing, or tightness in your chest			✓

This is not a complete list of side effects. For any unexpected effects while taking HELIXATE® FS, contact your doctor or pharmacist.

HOW TO STORE IT

Keep HELIXATE® FS in the refrigerator (2-8°C). You may store the powder at room temperature (up to 25°C) for 3 months. If the HELIXATE® FS is stored outside the refrigerator, please add the date removed from refrigeration and note a new expiry date on the carton and vial. The next expiry date is 3 months from the date product is removed from the refrigerator, or the previously stamped expiry date, whichever is shorter. Once HELIXATE® FS has been removed from refrigeration, it cannot be returned to the refrigerator. Store away from extreme light and do not use after the expiration date on the bottle. Do not freeze. Store the powder in the carton.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance by:

Toll-free telephone:	866-234-2345
Toll-free fax:	866-678-6789
Online:	www.healthcanada.gc.ca/medeffect
By email:	CanadaVigilance@hc-sc.gc.ca
By regular mail:	Canada Vigilance National Office Marketed Health Products Safety and Effectiveness Information Bureau Marketed Health Products Directorate Health Products and Food Branch Health Canada Tunney's Pasture, AL 0701C Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, CSL Behring Canada, Inc. at 613-783-1892.

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