PRODUCT MONOGRAPH

KOGENATE® FS

Antihemophilic Factor (Recombinant)

Formulated with Sucrose

With Vial Adapter

IV Injection, 250, 500, 1000, 2000, 3000 IU/vial

Coagulation Factor

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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, 3000 IU/vial	Sucrose Glycine Histidine Calcium chloride Sodium chloride Polysorbate 80 *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

DESCRIPTION

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

KOGENATE FS with vial adapter is a needle-less system provided with a prefilled syringe containing diluent for reconstitution.

INDICATIONS AND CLINICAL USE

KOGENATE 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). KOGENATE 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 persons with hemophilia.

When used as a regular prophylactic treatment, KOGENATE FS is 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**).

- to prevent or reduce the frequency of bleeding episodes in adults with hemophilia A (see Product Monograph Part II: **CLINICAL TRIALS** – **Adult Prophylaxis**).

Because KOGENATE FS showed comparable biological activity to other FVIII preparations, it should be used in the same manner as KOGENATE (Antihemophilic Factor [Recombinant]). This includes treatment of bleeding in certain patients with inhibitors to FVIII. In clinical studies of KOGENATE, some patients who developed inhibitors on study continued to manifest a clinical response when inhibitor titers 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**).

KOGENATE 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 KOGENATE 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 KOGENATE and other FVIII products has not identified differences between the elderly and younger patients. As with any patient receiving KOGENATE FS, dose selection for an elderly patient should be individualized.

Pediatrics (<18 years of age)

KOGENATE 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.

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

KOGENATE 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 KOGENATE 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 KOGENATE FS product in an appropriate container.

Persons with hemophilia who have 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 FVIII.

Catheter-related infections may be observed when KOGENATE FS is administered via central venous access devices (CVADs). These infections have not been associated with the product itself.

Carcinogenesis and Mutagenesis

See Product Monograph PART II: **TOXICOLOGY** – **Carcinogenicity/Mutagenesis** 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 KOGENATE (Antihemophilic Factor [Recombinant]), particularly in very young patients or patients who have previously reacted to other FVIII products (see **ADVERSE REACTIONS – Postmarket Adverse Drug Reactions**). Serious anaphylactic reactions require immediate emergency treatment with resuscitative measures such as the administration of epinephrine and oxygen.

In clinical studies, KOGENATE FS has been used in the treatment of bleeding episodes in 37 previously untreated patients (PUPs) and 23 minimally treated pediatric patients ([MTPs], 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%) PUPs and 4 out of 23 (17%) MTPs treated with KOGENATE 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 KOGENATE FS. It is also not known whether KOGENATE FS can cause fetal harm when administered to a pregnant woman or whether it affects reproduction capacity. KOGENATE FS should not be used during pregnancy unless the benefits clearly outweigh any potential risks. As the disease almost exclusively affects males, no females have been included in clinical studies.

Nursing Women

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

Geriatrics (>65 years of age)

Clinical studies with KOGENATE 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 KOGENATE and other FVIII products has not identified differences between the elderly and younger patients. As with any patient receiving KOGENATE FS, dose selection for an elderly patient should be individualized.

Pediatrics (<18 years of age)

KOGENATE 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. According to a published study (3), children in comparison to adults present higher FVIII clearance values and thus lower recovery of FVIII, which may be explained by differences in pharmacokinetics. This information should be taken into account when dosing or following FVIII levels in such a population (see **DOSAGE AND ADMINISTRATION** – **Dosing Considerations** and Product Monograph Part II: **CLINICAL TRIALS**).

Monitoring and Laboratory Tests

The clinical effect of KOGENATE FS is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more KOGENATE 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 ([PTPs], defined as having more than 100 exposure days), 451 adverse events were reported in the course of 24,936 infusions (1.8%). Only 24 events in 13 patients were considered to be at least remotely related to rFVIII-FS administration (0.1%, relative to the number of infusions). In clinical studies with 73 PTPs, one patient had a pre-existing inhibitor. In the other 72 patients, followed over four years, no de novo inhibitors were observed.

Table 2 – Adverse Events in PTPs With an Established Relationship to KOGENATE FS, FVIII Products, or Parenterally Administered Proteins

System Organ Class Adverse Event	Number of Patients With AE (%) (Total Number of Patients = 73)	AE per Infusion (%) (Total Number of Infusions = 24,936)
General Disorders and Administration Site Conditions		
Infusion site reactions	3 (4.1)	0.01
Skin and Subcutaneous Tissue Disorders		
Rash, Pruritis	6 (8.2)	0.02

In clinical studies with previously untreated patients (PUPs) and minimally treated (MTPs) pediatric patients, 726 adverse events were reported in the course of 9,389 infusions (7.7%). These included the expected complication of inhibitor development in 9 patients (see **WARNINGS AND PRECAUTIONS** – **Immune**).

Table 3 – Adverse Events in PUPs/MTPs With an Established Relationship to KOGENATE FS, FVIII Products, or Parenterally Administered Proteins

System Organ Class Adverse Event	Number of Patients with AE (%) (Total Number of Patients = 61)	AE per Infusion (%) (Total Number of Infusions = 9,389)
Blood and Lymphatic System Disorders		
Factor VIII inhibition	9 (15)[a]	N/A
General Disorders and Administration Site Conditions		
Infusion site reactions	4 (6.6)	0.04
Skin and Subcutaneous Tissue Disorders		
Rash, Pruritis	10 (16.4)	0.01

a Denominator for de novo inhibitors is N=60 since one patient had a preexisting inhibitor.

Postmarket Adverse Drug Reactions

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

Among patients treated with KOGENATE FS, cases of serious allergic/hypersensitivity reactions (which may include facial swelling, flushing, hives, blood pressure decrease, nausea, rash, restlessness, shortness of breath, tachycardia, tightness of the chest, tingling, urticaria, and

vomiting) have been reported, particularly in very young patients or patients who had previously reacted to other FVIII concentrates.

In extensive postregistration studies with KOGENATE FS involving more than 1000 patients, the following was observed: Less than 0.2% of 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.

Available registries have reported inhibitor rates for PUPs with severe hemophilia A in the range of 28 to 38% for FVIII products.

Table 4 – Postmarket Adverse Drug Reactions

System Organ Class	Adverse Event
Blood and Lymphatic System Disorders	FVIII inhibition
Skin and Subcutaneous Tissue Disorders[a]	Pruritis, urticaria, rash
General Disorders and Administration Site Conditions[a]	Infusion site reaction
	Pyrexia
Immune System Disorders	Anaphylactic reaction, other hypersensitivity signs and symptoms
Nervous System Disorders	Dysgeusia

a One patient may have reported more than one event

Since the launch of KOGENATE/KOGENATE FS, no confirmed cases of viral transmission have been reported.

DRUG INTERACTIONS

Drug-Drug Interactions

KOGENATE 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.

Drug-Lifestyle Interactions

No effects on the ability to drive or to use machines have been observed.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Each bottle of KOGENATE 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 the administration set provided to minimize losses of product due to adsorption and volume retention. KOGENATE FS should not be mixed with other medicinal products or infusion solutions.

According to a published study (3), children in comparison to adults present higher FVIII clearance values and thus lower recovery of FVIII which may be explained by differences in pharmacokinetics. This information should be taken into account when dosing or following FVIII levels in such a population.

Recommended Dose and Dosage Adjustment

The dosages described below are presented as general guidance. It should be emphasized that the dosage of KOGENATE 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 KOGENATE FS is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more KOGENATE 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 KOGENATE 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. KOGENATE 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 **DOSAGE AND ADMINISTRATION - 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 titer inhibitors (<10 B.U.) can be successfully treated with rFVIII-FS without a resultant anamnestic rise in inhibitor titer. 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 Activated Procoagulant Protein may be necessary for patients with anamnestic responses to FVIII treatment and/or high titer 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 (4) and is illustrated in the following examples.

Equation 1 – Calculation of KOGENATE 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 KOGENATE 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 5 – 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 (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)		
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. (5, 6) In children, the recommended dose for a regular prophylaxis schedule is 25 IU/kg of body weight every other day. (7) In adults, the recommended dose for routine prophylaxis is 25 IU/kg of body weight three times per week.

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

KOGENATE FS (Antihemophilic Factor [Recombinant] with vial adapter is a needle-less system that prevents needlestick injuries during reconstitution (see **WARNINGS AND PRECAUTIONS – General)**.

Rate of Administration

Data from clinical trials, including patients between 0-68 years old, shows that the entire dose is administered in a median of 5 minutes. The rate of administration, however, should be adapted to the response of each patient.

KOGENATE 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 KOGENATE 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 6 – 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

KOGENATE 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.

If any component of the package is opened or damaged, do not use this component. The reconstituted product must be filtered prior to administration to remove potential particulate matter in the solution. Filtering is achieved by using the vial adapter. After reconstitution, the product is to be used within 3 hours.

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. Remove protective cap from the vial (Figure 1: A). Aseptically cleanse the rubber stopper with alcohol, being careful not to handle the rubber stopper. Do not remove plunger rod until step 8.
3. Place product vial on a firm, non-skid surface. Peel off the paper cover on the vial adapter plastic housing. **Do not remove the adapter from the plastic housing**. Holding the adapter housing, place over the product vial and firmly press down (Figure 1: B).
4. The adapter will snap over the vial cap. **Do not remove the adapter housing at this step.**
5. Holding the syringe by the barrel, snap the syringe cap off the tip (Figure 1: C). **Do not touch the syringe tip with your hand or any surface**.
6. Now remove and discard the adapter housing (Figure 1: D).
7. Attach the prefilled syringe to the threaded vial adapter by turning clockwise (Figure 1: E).
8. Grasp the plunger rod by the top plate and remove from carton. **Avoid touching the sides and threads of the plunger rod.** Immediately attach the plunger rod by turning it firmly clockwise into the threaded syringe rubber stopper (Figure 1: F)
9. Inject the diluent by slowly pushing down on the plunger rod (Figure 1: G).
10. Swirl vial gently until all material is dissolved without creating excessive foaming (Figure 1: H). **Do not shake vial.** Be sure that the powder is completely dissolved. **Do not use solutions containing visible particles or that are cloudy.**
11. Withdraw solution into the syringe by holding the vial on end above the vial adapter and syringe (Figure 1: I) then draw the plunger rod out slowly and smoothly. Ensure that the entire content of the vial is drawn into the syringe.
12. With the plunger rod in place, remove the syringe from the vial adapter (the latter should remain attached to the vial).

For Bolus Injection

13. Attach the syringe to the administration set (made with microbore tubing) provided and inject intravenously within 3 hours of reconstitution (Figure 1: J). NOTE: follow instructions for infusion set provided. Use of other administration sets without microbore tubing may result in a larger retention of the solution within the administration set.
14. If the same patient is to receive more than one bottle, the diluent syringe provided should be used to reconstitute the powder in the product vials as described above. The reconstituted solutions should then be combined in a larger plastic syringe (not provided) and administered as usual.
15. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Figure 1 – Reconstitution Procedure

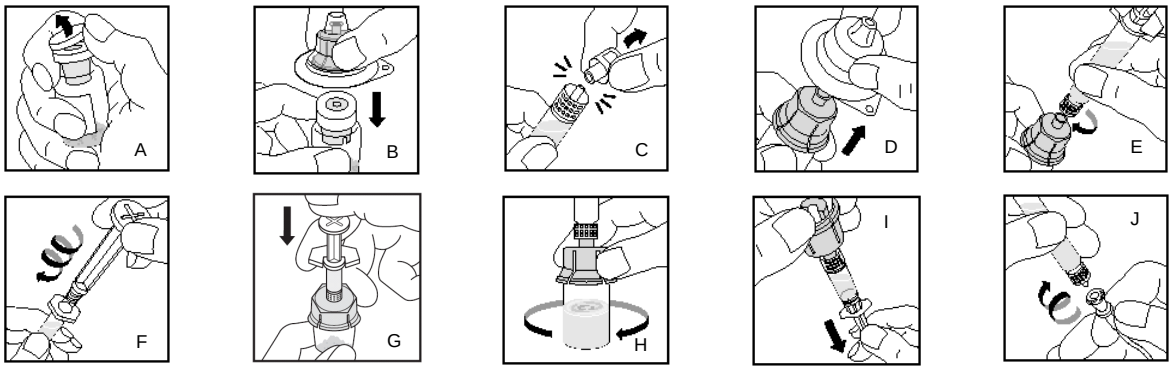

Table 7 – Reconsitiution of Parenteral Products

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
3000 IU	5.0 mL	5.0 mL	600 IU/mL

For Continuous Infusion

Reconstitute KOGENATE FS according to Steps 1-12 above. Continuous infusion of KOGENATE 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. During in vitro studies, reconstituted product for continuous infusion was shown to be stable for 24 hours at temperatures up to 30°C in polyvinyl chloride (PVC) bags. This should be kept in

mind if the continuous infusion is not intended to be started immediately after reconstitution. 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 6 for infusion rates.

Note: KOGENATE FS reconstituted with 2.5 or 5.0 mL Sterile Water for Injection should not be further diluted for continuous infusion.

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) is prolonged in people with hemophilia. Determination of aPTT is a conventional in vitro assay for biological activity of factor VIII. Treatment with KOGENATE FS normalizes the aPTT over the effective dosing period.

Pharmacokinetics

Initial pharmacokinetic studies were conducted in 35 patients, with severe hemophilia A. (8)

Absorption

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

Distribution

No specific distribution studies have been performed, however after administration of KOGENATE 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. **KOGENATE FS binds to its natural protein carrier vWF and is mostly confined into the vascular space.**

Metabolism

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

Excretion

After administration of KOGENATE 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

KOGENATE FS (Antihemophilic Factor [Recombinant]) should be stored under refrigeration (2°C-8°C). Do not use beyond the expiration date indicated on the bottle. Storage of lyophilised powder at room temperature up to 25°C for 12 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 12 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 (within 3 hours) for direct syringe injection. For continuous infusion, stability has been demonstrated for 24 hours at 30°C in polyvinyl chloride (PVC) bags.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

KOGENATE FS (Antihemophilic Factor [Recombinant]) with a vial adapter, is supplied in the following single use bottles. A prefilled diluent syringe containing Sterile Water for Injection,

EP, USP for reconstitution, a sterile vial adapter, a sterile administration set, two alcohol swabs, one sterile bandage, and one sterile cotton pad are provided.

Table 8 – KOGENATE FS Vial Sizes

Product Code	Approximate Factor VIII Activity	Diluent
XXXXX	250 IU	2.5 mL
XXXXX	500 IU	2.5 mL
81791458	1000 IU	2.5 mL
81791512	2000 IU	5.0 mL
XXXXX	3000 IU	5.0 mL

Each vial of KOGENATE 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 9 – KOGENATE FS Inactive Ingredients

Inactive Ingredient/Excipient	250 IU, 500 IU, 1000 IU Vial Size	2000 IU, 3000 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. KOGENATE FS must be administered by the intravenous route.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	KOGENATE FS
Common name:	Antihemophilic Factor [Recombinant]

Product Characteristics

KOGENATE 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. No human or animal proteins, such as albumin, are added during the purification and formulation processes of KOGENATE FS.

KOGENATE 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 KOGENATE 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 KOGENATE 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

Previously Treated Patients (PTPs)

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 treated up to 54 months in studies with rFVIII-FS in Europe and North America. A total of 24,924 infusions (or 45 million units) of rFVIII-FS were administered during the studies. A total of 5,684 bleeding episodes were treated during the studies. The majority of bleeding episodes (92.7%) were treated successfully with one or two infusions, with a median dosage of approximately 32.5 and 29.6 IU/kg per treatment infusion, in Europe and North America, respectively. Prophylactic treatment accounted for 76% of infusions administered during the studies. Thirty patients have received rFVIII-FS for 41 surgical procedures (16 minor and 25 major). Hemostasis was satisfactory in all cases. One out of the 73 PTPs started the study with a pre-existing inhibitor. Excluding this patient, zero patients developed inhibitors. (1, 8, 9)

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

Study Results

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

Previously Untreated and Minimally Treated Patients

In completed clinical studies, KOGENATE FS has been used in the treatment of bleeding episodes in previously untreated patients (PUPs) and minimally treated pediatric patients (MTPs). In completed studies, 37 PUPs and 24 MTPs have been treated with 9,419 infusions of KOGENATE FS corresponding to a total of 7.5 million IU for a follow-up duration up to 3.1 years and a median of 115 exposure days. A total of 1047 bleeding episodes were treated effectively with one or two infusions of rFVIII-FS in 88.1% of cases. A total of 29 surgical procedures were performed in 23 patients. Hemostasis was satisfactory in all cases. One out of the 61 PUPs/MTPs started the study with a pre-existing inhibitor. Excluding this patient, 9 out of 60 (15%) patients developed inhibitors after a median number of 7 exposure days (range of 2-16 exposure days). (1, 2)

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. (7) 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)

Adult Prophylaxis

A 3-year, multicenter, open-label, parallel-group, prospective, randomized, controlled clinical study of the effect of regular prophylaxis with KOGENATE FS versus on-demand use on bleeding frequency and joint outcomes was performed in adults and adolescents with severe hemophilia A (FVIII level < 1 IU/dL). (10)

Eighty-four PTPs, aged 15 to 50 years (mean: 30.6 years), were randomized 1:1 to either a standard prophylaxis regimen (25 IU/kg three times a week) or on-demand use of KOGENATE FS. Escalation of the prophylaxis dose by 5 IU/kg/infusion after Years 1 and 2, up to a maximum of 35 IU/kg/infusion, was allowed. Baseline characteristics (eg, demographics, disease state) were similar between the two treatment groups. The median number of bleeds in the year before enrollment for all 84 patients was 18.

The primary endpoint, bleeding frequency, was analyzed in the intent-to-treat population after a median follow-up period of about 1.4 years. Prophylactic treatment led to a statistically significant and clinically meaningful decrease in bleeds (P < 0.0001), as well as in a number of other bleeding endpoints (see Table 10) compared to on-demand treatment. The median annual bleed rate (bleeds/subject/year) in the on-demand group was 33 versus zero in the prophylaxis group. All of the 42 patients in the on-demand group had at least one bleeding event, and only 21 of the 42 patients in the prophylaxis group had a bleeding event. For these patients who had at least one bleeding event, the median time to first bleed was 3.3 days in the on-demand group and 87.9 days in the prophylaxis group.

Twenty-two patients from the prophylaxis group (52%) and one patient from the on-demand group (2%) did not experience a bleeding event (defined as spontaneous or traumatic bleed), and 12 prophylaxis patients (29%) and 1 on-demand patient (2%) experienced only 1-2 bleeds.

There was a 94% reduction in the mean annual bleed rate: 36.89 bleeds/patient/year in the on-demand group versus 2.24 bleeds/patient/year in the prophylaxis group. Those patients who received prophylaxis experienced 15.2 times fewer bleeds compared to patients treated on-demand. There was a 93% reduction in the mean annual joint bleed rate: 29 bleeds/patient/year in the on-demand group versus 2 bleeds/patient/year in the prophylaxis group.

Prophylactic compared to on-demand treatment with KOGENATE FS resulted in large reductions in bleeding regardless of baseline characteristic examined including age, bleeding history, and presence or absence of target joints (see Table 11). In particular, the median annual bleed rate among on-demand patients >30 years of age was 31, compared to 0 among prophylaxis patients in the same age group.

Table 10 - Summary of Bleeds by Type – ITT Population

		On-Demand N = 42	**Prophylaxis N = 42**
Number of Total Bleeds[a]	Median	54.5	0
	Sum	2214	175
Annualized number of bleeds (inclusive of total bleeds[a] + unknown + other)	Mean	38.90	2.55
	SD	23.52	5.46
	Median	37.47	0.33
	Min	1.9	0.0
	Max	106.2	21.9
Annualized number of spontaneous bleeds	Mean	23.80	1.29
	SD	19.58	3.08
	Median	19.77	0.0
	Min	0.0	0.0
	Max	84.1	15.0
Annualized number of trauma bleeds	Mean	13.09	0.95
	SD	17.67	2.69
	Median	7.94	0.0
	Min	0.0	0.0
	Max	99.9	15.3
Annualized number of joint bleeds	Mean	29.20	1.90
	SD	20.59	4.70
	Median	24.39	0.0
	Min	0.0	0.0
	Max	80.1	18.4

a Total bleeds = Spontaneous bleeds + Traumatic bleeds

Table 11 - Annual Bleeds Overall and by Baseline Characteristic

		On-Demand			Prophylaxis		
		N	Median	% with 0 bleeds	N	Median	% with 0 bleeds
Overall		42	28	2.4	42	0	52
Age	<18	1	21.71	0	2	0	100
	18 to <30	21	43.8	4.8	19	0.71	42.1
	≥30	20	30.7	0	21	0	57.1
Number of bleeds in previous year	<15	10	24.42	0	14	0	69.2
	≥15	32	34.62	2.9	27	0.69	44.8
Presence of target joints	No	11	17.63	9.1	14	0	57.1
	Yes	31	43.8	0	28	0.33	50.0

The most common self-rating of bleed severity among prophylaxis patients was mild (44%), compared to moderate (58%) for on-demand patients (Table 12).

Table 12 – Patients' Self-Rating of Bleed Severity

	On-Demand	Prophylaxis
Bleed severity		
Number of bleeds	2363 (100%)	196 (100%)
Missing	150 (6.3%)	24 (12.2%)
Mild	396 (16.8%)	87 (44.4%)
Moderate	1364 (57.7%)	71 (36.2%)
Severe	453 (19.2%)	14 (7.1%)

Bleeding episodes were treated effectively with 1 or 2 infusions of KOGENATE FS. Among prophylaxis patients, this level of hemostasis was achieved with a moderate exposure to KOGENATE FS: 4patients had 2.84 infusion days per week, and the median dose per prophylaxis infusion was 27 IU/kg.

No inhibitors were detected in this study. The adverse event profile was consistent with previous studies.

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) is prolonged in people with hemophilia. Determination of aPTT is a conventional in vitro assay for biological activity of factor VIII. Treatment with KOGENATE FS normalizes the aPTT over the effective dosing period.

Absorption and Bioavailability

KOGENATE 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 37 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 KOGENATE 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. **KOGENATE FS binds to its natural protein carrier vWF and is mostly confined into the vascular space.**

Metabolism

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

Excretion

After administration of KOGENATE 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 titers 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 titers 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 titer 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 titer to rFVIII-FS by Day 33. There were no apparent adverse effects in those rabbits that developed a titer. 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 titer at Day 33. No adverse effects were seen in dogs that developed an antibody titer.

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 did not 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 due to the immune response to heterologous proteins in all non human mammalian species.

REFERENCES

1. Kreuz W, Gill JC, Rothschild C, Manco-Johnson MJ, Lusher JM, Kellermann E, et al. Full-length sucrose-formulated recombinant factor VIII for treatment of previously untreated or minimally treated young children with severe haemophilia A: results of an international clinical investigation. Thromb Haemost. 2005 Mar;93(3):457-67.

2. Lusher J, Abildgaard C, Arkin S, Mannucci PM, Zimmermann R, Schwartz L, et al. Human recombinant DNA-derived antihemophilic factor in the treatment of previously untreated patients with hemophilia A: final report on a hallmark clinical investigation. J Thromb Haemost. 2004 Apr;2(4):574-83.

3. Barnes C, Lillicrap D, Pazmino-Canizares J, Blanchette V, Stain A, Clark D, et al. Pharmacokinetics of recombinant factor VIII (Kogenate FS) in children and causes of inter-patient variability. Haemophilia. 2006;12(Suppl. 4):40-9.

4. Abildgaard CF, Simone JV, Corrigan JJ, Seeler RA, Edelstein G, Vanderheiden J, et al. Treatment of hemophilia with glycine-precipitated factor 8. N Engl J Med. 1966 Sep 1;275(9):471-5.

5. Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. J Intern Med. 1992 Jul;232(1):25-32.

6. Carcao MD, Aledort L. Prophylactic factor replacement in hemophilia. Blood Rev. 2004 Jun;18(2):101-13.

7. 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 Aug 9;357(6):535-44.

8. Abshire TC, Brackmann HH, Scharrer I, Hoots K, Gazengel C, Powell JS, et al. Sucrose formulated recombinant human antihemophilic factor VIII is safe and efficacious for treatment of hemophilia A in home therapy--International Kogenate-FS Study Group. Thromb Haemost. 2000 Jun;83(6):811-6.

9. Scharrer I, Brackmann HH, Sultan Y, Abshire T, Gazengel C, Ragni M, et al. Efficacy of a sucrose-formulated recombinant factor VIII used for 22 surgical procedures in patients with severe haemophilia A. Haemophilia. 2000 Nov;6(6):614-8.

10. Manco-Johnson MJ, Kempton CL, Reding MT, Lissitchkov T, Goranov S, Gercheva L, et al. Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART). J Thromb Haemost. 2013 Jun;11(6):1119-27.

PART III: CONSUMER INFORMATION

KOGENATE® FS

Antihemophilic Factor (Recombinant)

Formulated with Sucrose

With Vial Adapter

This leaflet is Part 3 of a three-part "Product Monograph" published when *KOGENATE 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 *KOGENATE FS*. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

KOGENATE 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. KOGENATE 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.

When used as a regular prophylactic treatment, KOGENATE FS is indicated to prevent the occurrence of spontaneous hemorrhagic episodes and to prevent joint damage in children. KOGENATE FS is also indicated to prevent and control bleeding in adults with hemophilia A when used regularly.

What it does:

KOGENATE 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, KOGENATE FS gives them additional Factor VIII to help prevent and/or control bleeding. KOGENATE FS is given directly into the blood through an injection in a vein.

When it should not be used:

KOGENATE 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

KOGENATE FS does not contain any preservatives.

What dosage forms it comes in:

KOGENATE FS is a dried product powder available in vials containing 250 IU*, 500 IU, 1000 IU, (with 2.5 mL Sterile Water for Injection), 2000 IU, and 3000 IU (with 5.0 mL Sterile Water for Injection), supplied with a sterile vial adapter and a sterile administration set. A prefilled syringe containing Sterile Water for Injection for reconstitution, a sterile administration set, two alcohol swabs, one sterile bandage, and one sterile cotton pad are also provided. After reconstitution, KOGENATE 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 than 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 KOGENATE FS talk to your doctor or pharmacist if

- you are allergic to mouse or hamster protein, or any of the ingredients in KOGENATE FS.
- you have had inhibitor development in the past.
- you have been told you have heart disease or are at risk for heart disease.
- 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 KOGENATE 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.
- The regular prophylaxis schedule for adults is 25 IU/kg of body weight three times per week.

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, some side effects included reactions at the injection site, rash, and itchy skin.

In patients who had no previous treatment with Factor VIII, some side effects included formation of inhibitors to Factor VIII, reactions at the injection site, rash, and itchy skin.

You may find that more KOGENATE 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 seek emergency medical treatment
	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 *KOGENATE FS*, contact your doctor or pharmacist.

HOW TO STORE IT

Keep KOGENATE FS with vial adapter in the refrigerator (2°C-8°C). You may store the powder at room temperature up to 25°C for 12 months. If the KOGENATE 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 12 months from the date product is removed from the refrigerator, or the previously stamped expiry date, whichever is shorter. Once KOGENATE 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

Canada Vigilance Program

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online:	www.healthcanada.gc.ca/medeffect
Call toll-free at:	1-866-234-2345
Complete a Canada Vigilance Reporting Form and:	
Fax toll-free to:	1-866-678-6789, or
Mail to:	Canada Vigilance Program Health Canada Postal Locator 0701E Ottawa ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada website at: www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Bayer Inc.

You can report any suspected adverse reactions associated with the use of health products to Bayer Inc. by:

- Toll-free telephone: 1-800-265-7382
- Email: canada.medinfo@bayer.com
- Regular Mail: Bayer Inc.
  77 Belfield Road
  Toronto, Ontario
  M9W 1G6
  Canada

NOTE: Should you require information related to the management of the side effect, please contact your health professional. Bayer Inc. does not provide medical advice.

MORE INFORMATION

For more information, please contact your health professional or pharmacist first, or Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

This document plus the full product monograph, prepared for health professionals can be obtained at www.bayer.ca or by contacting the sponsor at the above-mentioned phone number and email address.

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