DESCRIPTION
Kogenate® FS Antithrombotic Factor (Recombinant) is a sterile, stable, purified, nonpyrogenic, dried concentrate that has been manufactured using recombinant DNA technology. Kogenate® FS is intended for the treatment of bleeding disorders in patients with hemophilia A. It is administered by intravenous infusion and is reconstituted in a sterile, nonpyrogenic, pH-balanced dextrose solution.

Kogenate® FS is a genetically engineered form of human FVIII, produced in human cells transformed with a plasmid providing a structural gene for FVIII. Its amino acid sequence and position of glycosylation are identical to those found in plasma-derived FVIII, based on the overall antigenic properties of the two preparations. Kogenate® FS is a single-chain protein, with a molecular weight of 180,000 Daltons and a plasmid with the gene for Factor VIII. The gene is inserted into a bacterial plasmid, and the bacteria are grown to produce the recombinant Factor VIII. The Factor VIII is then purified from the bacteria and packaged in vials.

The Factor VIII concentrate is then reconstituted in a sterile, nonpyrogenic solution and administered intravenously to patients with hemophilia A.

CLINICAL PHARMACOLOGY
Kogenate® FS is formulated with sucrose (0.9–1.3%), glycine (21–25 mg/mL), and histidine (18–23 mM) as stabilizers. In addition, phosphate buffer (2 mmol/L) at pH 7.0 is used as a stabilizer as Kogenate® FS is a pH-stable product. The solution of Kogenate® FS contains approximately 100,000 IU of FVIII activity, which is approximately equal to the level of FVIII activity found in 1 mL of fresh pooled human plasma.

Kogenate® FS is administered intravenously as a single dose with a mean of approximately 13 hours, which has previously been shown to be similar to the average duration of effect of KOGENA TE. The duration of effect of Kogenate® FS is approximately equal to the duration of effect of KOGENA TE.

Adults should be advised to discontinue use of the product and contact their physician if such symptoms occur.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
In vitro evaluation of the mutagenic potential of FVIII failed to demonstrate reverse mutation or dominant lethal effects at doses greater than the maximum expected clinical dose. In vivo evaluation of FVIII in animals using doses ranging between 10 and 40 times the expected clinical dose for adults did not reveal any significant carcinogenic potential. Long-term investigations of carcinogenic potential in animals have not been performed.

Pediatric Use
Kogenate® FS is appropriate for use in pediatric patients of all ages, including neonates, infants, and children. Safety and effectiveness have been established for the treatment of bleeding episodes in previously treated pediatric patients and minimally treated pediatric patients (n = 62). Kogenate® FS is similar to KOGENA TE® Antithrombotic Factor (Recombinant) in its biological activity and may be used in pediatric patients in the same manner as KOGENA TE.

Geriatric Use
Clinical studies with Kogenate® FS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently to Kogenate® FS compared to younger patients. There was no evidence of diminished efficacy in elderly patients who were treated with Kogenate® FS, and no evidence of increased sensitivity of the elderly to Kogenate® FS.

Pregnancy Category C
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 can affect reproduction capacity. Kogenate® FS should be used during pregnancy and lactation only if clearly indicated.

ADVERSE REACTIONS
The following are events principally derived from post-marketing experience and publications, and accurate rate estimates are generally not possible. Among patients treated with its predecessor product KOGENA TE® Antithrombotic Factor (Recombinant), very rare cases of serious allergic reactions and anaphylactic reactions have been reported, particularly in very young patients or patients who had previously reacted to other FVIII concentrates (see ADVERSE REACTIONS—Post-marketing experience). Serious anaphylactic reactions require immediate emergency treatment and supportive measures such as administration of epinephrine and oxygen.

Formation of Antibodies to Mouse and Hamster Protein
Assays to detect seroconversion to mouse and hamster protein were conducted on all patients in clinical trials. No patient developed antibodies to mouse or hamster protein.

Kogenate® FS Antithrombotic 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. It is not known whether the use of the classical purification methods of ion exchange chromatography, monoclonal antibody immunoaffinity chromatography, and other chromatographic steps designed to purify recombinant FVIII and remove contaminating substances.

Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental model of transmissible spongiform encephalopathy (TSE), defined as a model for the vCJD and CJD agents.26–27 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. TSE reduction steps included the Fraction II + III separation step for Human Plasma Protein Solution (6.0 log10) and an anion exchange chromatography step (3.6 log10). Thus, the steps are reasonable grounds for believing that low levels of CJD/CJD agent infectivity, if present in the starting material, would be removed.

Kogenate® FS is formulated with sucrose (0.9–1.3%), glycine (21–25 mg/mL), and histidine (18–23 mM) as stabilizers. In addition, phosphate buffer (2 mmol/L) at pH 7.0 is used as a stabilizer as Kogenate® FS is a pH-stable product. The solution of Kogenate® FS contains approximately 100,000 IU of FVIII activity, which is approximately equal to the level of FVIII activity found in 1 mL of fresh pooled human plasma.

Kogenate® FS is administered intravenously as a single dose with a mean of approximately 13 hours, which has previously been shown to be similar to the average duration of effect of KOGENA TE. The duration of effect of Kogenate® FS is approximately equal to the duration of effect of KOGENA TE.

CONTRAINdications
Known intolerance or allergic reactions to constituents of the preparation.

Kogenate® FS may be a contraindication to the use of Kogenate® FS.

Warnings
None.

Precautions
General
Kogenate® FS Antithrombotic 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.

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 hemophilia during their first years of treatment, or in patients of any age who have received little or no previous treatment with FVIII. Neutralization of FVIII activity may occur at any time in the treatment of a patient with hemophilia A. Patients treated with any AHF preparation, including Kogenate® FS, should be carefully monitored for the development of antibodies to FVIII by appropriate clinical observation and laboratory tests, according to the recommendation of the patient’s hemophilia treatment center.

Among patients treated with antithrombotic factor concentrates, cases of hypotension, urticaria, and chills have been reported. These adverse events are associated with high fibrinogen levels.13 Very rare cases of allergic and anaphylactic reactions have been reported with the predecessor product KOGENA TE® Antithrombotic Factor (Recombinant), particularly in patients who have previously reacted to other FVIII concentrates (see ADVERSE REACTIONS—Post-marketing experience). Serious anaphylactic reactions require immediate emergency treatment and supportive measures such as administration of epinephrine and oxygen.

Kogenate® FS Antithrombotic 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.
Calculation of Dosage
The in vivo percent elevation in FVIII level can be estimated by multiplying the dose of Kogenate® FS Antihemophilic Factor (Recombinant) per kilogram of body weight (IU/kg) by 2% per IU per kg. This method of calculation is based on clinical findings with the use of plasma-derived and recombinant AHF products and is illustrated in the following examples:

Expected % factor VIII increase = \# units administered × 2%/IU/kg

Example for a 70 kg adult:

\[ \frac{1400 \text{ IU}}{70 \text{ kg}} \times 2\% = 40\% \]

or

body weight (kg) = desired % FVIII increase

Dosage required (IU) = 2%/IU/kg

Example for a 15 kg child:

\[ \frac{15 \text{ kg} 	imes 100\%}{2\%/\text{IU/kg}} = 750 \text{ IU required} \]

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

<table>
<thead>
<tr>
<th>Hemorrhagic event</th>
<th>Therapeutically necessary plasma level of FVIII activity</th>
<th>Dosage necessary to maintain the therapeutic plasma level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor hemorrhage (superficial, early hematomas)</td>
<td>20–40%</td>
<td>10–20 IU per kg Repeat dose if evidence of further bleeding.</td>
</tr>
<tr>
<td>Moderate to major hemorrhage (hematomas into the oral cavity, definite hemorrhathes, known trauma)</td>
<td>30–60%</td>
<td>15–30 IU per kg Repeat one dose at 12–24 hours if needed.</td>
</tr>
<tr>
<td>Major to lethal-threatening hemorrhage (intracranial, intraabdominal or intrathoracic hemorrhages, gastrointestinal bleeding, central nervous system bleeding, bleeding in the retroperitoneal or retroperitoneal spaces, or ilipsoas sheath)</td>
<td>80–100%</td>
<td>Initial dose 40–50 IU per kg Repeat dose 20–25 IU per kg every 8–12 hours.</td>
</tr>
</tbody>
</table>

**Prophylaxis**

AHF concentrates may also be administered on a regular schedule for prophylaxis of bleeding, as reported by Nilsson et al.10

**Instructions for Use**

Reconstitution, product administration, and handling of the administration set and needles must be done with care. 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 Antihemophilic Factor (Recombimant) product, in accordance with biohazard procedures.

Reconstitution

Always wash your hands before performing the following procedures:

**Vacuum Transfer**

1. Warm the unopened diluent and the concentrate to a temperature not to exceed 37°C, 99°F.
2. After removing the plastic flip-top caps (Fig. A), aseptically cleanse the rubber stoppers of both bottles with alcohol, being careful not to handle the rubber stopper.
3. Remove the protective cover from one end of the plastic transfer needle cartridge and penetrate the rubber seal on the concentrate bottle (Fig. C) with the needle at an angle.
4. The vacuum will draw the diluent into the concentrate bottle. Hold the diluent bottle at an angle to the concentrate bottle in order to direct the jet of diluent against the wall of the concentrate bottle (Fig. C). Avoid excessive foaming. If the diluent does not get drawn into the bottle, there is insufficient vacuum and the product should not be used.
5. After removing the diluent bottle and transfer needle (Fig. D), swirl until completely dissolved without creating excessive foaming (Fig. E).
6. Re-swab top of reconstituted Kogenate FS bottle with alcohol. Allow the stopper to air dry.
7. After the concentrate powder is completely dissolved, withdraw solution into the syringe through the filter needle that is supplied in the package (Fig. F). Replace the filter needle with the administration set provided and inject intravenously. **NOTE:** See accompanying instructions for Infusion Set with Filter.
8. 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 filter needle before attaching the vein needle.
9. 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 filter needle before attaching the vein needle.
10. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**Rate of Administration**

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

**HOW SUPPLIED**

Kogenate® FS Antithemophilic Factor (Recombimant) is supplied in the following single use bottles. A suitable volume of Sterile Water for Injection, USP, a sterile double-ended transfer needle, a sterile filter needle, and a sterile administration set are provided.

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Approximate FVIII Activity (IU)</th>
<th>Diluent (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0026-0372-20</td>
<td>250 IU</td>
<td>2.5</td>
</tr>
<tr>
<td>0026-0372-30</td>
<td>500 IU</td>
<td>2.5</td>
</tr>
<tr>
<td>0026-0372-50</td>
<td>1000 IU</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**STORAGE**

Kogenate FS should be stored under refrigeration (2–8°C; 36–46°F). Storage of lyophilized powder at room temperature (up to 25°C or 77°F) for 3 months, such as in home treatment situations, may be done. Freezing must be avoided. Do not use beyond the expiration date indicated on the bottle. Protect from extreme exposure to light and store the lyophilized powder in the canistor prior to use.

**REFERENCES**