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Antihemophilic Factor (Recombinant)

Kogenate® FS

Formulated with Sucrose

DESCRIPTION

Kogenate® FS Antihemophilic Factor (Recombinant) is a sterile, stable, purified, nonpyrogenic, dried concentrate that has been manufactured using recombinant DNA technology. Kogenate FS is intended for use in the treatment of classical hemophilia (hemophilia A), and is produced by Baby Hamster Kidney (BHK) cells into which the human factor VIII (FVIII) gene has been introduced.[1] The cell culture medium contains Human Plasma Protein Solution (HPPS) and recombinant insulin, but does not contain any proteins derived from animal sources. Kogenate FS is a highly purified glycoprotein consisting of multiple peptides including an 80 kD and various extensions of the 90 kD subunit. It has the same biological activity as FVIII derived from human plasma. Compared to its predecessor product KOGENATE® Antihemophilic Factor (Recombinant), Kogenate FS incorporates a revised purification and formulation process that eliminates the addition of Albumin (Human).

The purification process includes an effective solvent/detergent virus inactivation step in addition to the use of the classical purification methods of ion exchange chromatography, monoclonal antibody immunoaffinity chromatography, along with 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 agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.[15–27] 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 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 (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.

Kogenate FS is formulated with sucrose (0.9–1.3%), glycine (21–25 mg/mL), and histidine (18–23 mM) as stabilizers in the final container in place of Albumin (Human) as used in KOGENATE, and is then lyophilized. The final product also contains calcium chloride (2–3 mM), sodium (27–36 mEq/L), chloride (32–40 mEq/L), polysorbate 80 (64–96 µg/mL), imidazole (NMT 20 µg/1000 IU), tri-n-butyl phosphate (NMT 5 µg/1000 IU), and copper (NMT 0.6 µg/1000 IU). The product contains no preservatives. The amount of sucrose in each vial is 28 mg. Intravenous administration of sucrose contained in Kogenate FS will not affect blood glucose levels.

Each vial of Kogenate FS contains the labeled amount of recombinant FVIII 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.

Kogenate® FS Antihemophilic Factor (Recombinant) must be administered by the intravenous route.

CLINICAL PHARMACOLOGY

Pharmacokinetic studies were conducted in 20 patients with severe hemophilia A in North America. In this comparative pharmacokinetic study, Kogenate FS was shown to be similar to its predecessor product KOGENATE® Antihemophilic Factor (Recombinant) (rFVIII). Mean FVIII recovery measured 10 minutes following infusion was 2.1 ± 0.3 %/IU/kg for Kogenate FS and 2.4 ± 0.7 %/IU/kg for KOGENATE. The two recoveries were not statistically different (confidence interval 0.815–1.01). The mean biological half-life of recombinant FVIII formulated with sucrose (rFVIII-FS) is similar to KOGENATE with a mean of approximately 13 hours, which has previously been shown to be similar to plasma-derived Antihemophilic Factor (AHF). The activated partial thromboplastin time shortened appropriately with both rFVIII and rFVIII-FS. The recovery and half-life 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 2.1%/IU/kg, which was unchanged from FVIII recovery determined at baseline and at weeks 4 and 12.

Seventy-one patients with severe hemophilia A, ages 12–59, who had been previously treated with other recombinant and with plasma-derived AHF products, were enrolled in 6-month studies of home therapy with rFVIII-FS in Europe and North America. A total of 3995 infusions have been administered under this portion of the study, or 7.4 million units of rFVIII-FS. Treatment of 659 bleeding episodes during the study period required 951 infusions of rFVIII-FS. The majority of bleeding episodes (89.5%) were treated successfully with one or two infusions, using a mean dosage of approximately 28 IU/kg per treatment infusion. Regularly scheduled treatment accounted for 76% of infusions administered on study. Nine patients have received rFVIII-FS on 11 occasions for surgical procedures. The procedures included removal of a brain tumor, 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.

In clinical studies, Kogenate FS has been used in the treatment of bleeding episodes in previously untreated patients (PUPs) and minimally treated (MTP) pediatric patients. In ongoing studies, 61 PUPs/MTPs have been treated with Kogenate FS. Bleeding episodes were treated effectively with one or two infusions of rFVIII-FS. Ten patients have developed inhibitors. In these trials, approximately half of the patients have achieved 20 or more exposure days, and the incidence of inhibitor formation (15%) is consistent with that observed in other pediatric studies using plasma-derived and recombinant factor VIII products.[2-5]

INDICATIONS AND USAGE

Kogenate FS is indicated for the treatment of classical hemophilia (hemophilia A) in which there is a demonstrated deficiency of activity of the plasma clotting factor 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 hemophiliacs.

In clinical studies with the predecessor product KOGENATE, some patients who developed inhibitors on study continued to manifest a clinical response when inhibitor titers were less than 10 Bethesda Units (BU) 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 circulating FVIII levels after treatment (see **DOSAGE AND ADMINISTRATION**). Because Kogenate FS has similar biological activity to KOGENATE it can be used in the same manner.

Kogenate FS does not contain von Willebrand's factor and therefore is not indicated for the treatment of von Willebrand's disease.

CONTRAINDICATIONS

Known intolerance or allergic reactions to constituents of the preparation.

Known hypersensitivity to mouse or hamster protein may be a contraindication to the use of Kogenate FS.

WARNINGS

None.

PRECAUTIONS

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.

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 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 antihemophilic factor concentrates, cases of hypotension, urticaria, and chest tightness in association with hypersensitivity reactions have been reported in the literature.[11-13] 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 concentrates (see ADVERSE REACTIONS—Post-marketing experience). Serious anaphylactic reactions require immediate emergency treatment with resuscitative measures such as the 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 studies. No patient has developed specific antibodies to these proteins after commencing study, 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 (e.g., 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.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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.

Pediatric Use

Kogenate FS is appropriate for use in pediatric patients of all ages, including neonates, infants, children, and adolescents. Safety and efficacy studies have been performed in previously untreated and minimally treated pediatric patients (n = 62). Kogenate FS is similar to KOGENATE® Antihemophilic Factor (Recombinant) in its biological activity and may be used in pediatric patients in the same manner as KOGENATE.

Geriatric Use

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 AHF 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.

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 affect reproduction capacity. Kogenate FS should be used during pregnancy and lactation only if clearly indicated.

ADVERSE REACTIONS

During the clinical studies conducted in previously treated patients (PTPs), 109 adverse events were reported in the course of 4160 infusions (2.6%). Only 13 events were reported by the investigator as at least remotely related to study drug. Another 7 events were nonassessable. Thus 20 events in 11 patients were considered to be either nonassessable or at least remotely related to Kogenate® FS Antihemophilic Factor (Recombinant) administration, for an incidence of 0.5% relative to the number of infusions administered. Events that were at least remotely drug-related included: local injection site reactions (2), dizziness (2), rash (2), unusual taste in the mouth (1), mild increase in blood pressure (1), pruritus (1), depersonalization (1), nausea (1), and rhinitis (1). No FVIII inhibitors have developed in the 72 PTPs with severe hemophilia A who have received Kogenate FS for a mean of 54 exposure days.

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 10 patients discussed under **CLINICAL PHARMACOLOGY**), a forearm bleed following venipuncture, constipation, adenopathy, rash, anemia and pallor in one inhibitor patient with gastroenteritis, and serous otitis media.

Post-marketing experience

The following events are principally derived from post-marketing experience and publications,[14] and accurate rate estimates are generally not possible. Among patients treated with its predecessor product KOGENATE® Antihemophilic 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. 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 Kogenate FS Antihemophilic Factor (Recombinant), Formulated with Sucrose, it is likely that these may also occur. Rare cases of dyspnea have been reported with Kogenate FS.

DOSAGE AND ADMINISTRATION

Each bottle of Kogenate FS has the rFVIII potency in international units stated on the label based on the one-stage assay methodology. The reconstituted product must be administered within 3 hours after reconstitution. It is recommended to use the administration set provided.

GENERAL APPROACH TO TREATMENT AND ASSESSMENT OF TREATMENT EFFICACY

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 FVIII is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more FVIII than 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 FVIII could be extremely variable among different patients, and the optimal treatment can be determined only by the clinical response.

Some patients with low-titer inhibitors (< 10 BU) can be successfully treated with FVIII preparations without a resultant anamnestic rise in inhibitor titer.[6] FVIII levels and clinical response to treatment must be assessed to insure adequate response. Use of alternative treatment products, such as Factor IX Complex concentrates, 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-titer inhibitors.

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[7-9] and is illustrated in the following examples:

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

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

or

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

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

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

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) **Surgery** (minor surgical procedures)	30–60%	15–30 IU per kg Repeat one dose at 12–24 hours if needed.
Major to life-threatening hemorrhage (intracranial, intraabdominal or intrathoracic hemorrhages, gastrointestinal bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces, or iliopsoas sheath) **Fractures** **Head trauma**	80–100%	Initial dose 40–50 IU per kg Repeat dose 20–25 IU per kg every 8–12 hours.
Surgery Major surgical procedures	~ 100%	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.

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 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 Antihemophilic Factor (Recombinant) product, in accordance with biohazard procedures.

Reconstitution

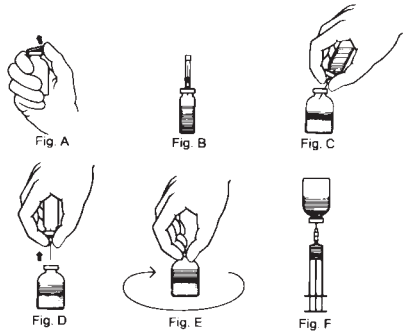
Always wash your hands before performing the following procedures:

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 stopper of the diluent bottle (Fig. B).
4. Remove the remaining portion of the *protective cover*, invert the diluent bottle and penetrate the rubber seal on the concentrate bottle (Fig. C) with the needle at an angle.
5. 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.
6. After removing the diluent bottle and transfer needle (Fig. D), swirl until completely dissolved without creating excessive foaming (Fig. E).
7. Re-swab top of reconstituted Kogenate FS bottle with alcohol. Allow the stopper to air dry.
8. 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.
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 Antihemophilic Factor (Recombinant) 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.

NDC Number	Approximate FVIII Activity (IU)	Diluent (mL)
0026-0372-20	250	2.5
0026-0372-30	500	2.5
0026-0372-50	1000	2.5

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 carton prior to use.

CAUTION

℞ only

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