

# Antihemophilic Factor (Recombinant)

---

## KOGENATE®

---

### DESCRIPTION

Antihemophilic Factor (Recombinant), KOGENATE® is a sterile, stable, purified, nonpyrogenic, dried concentrate which has been manufactured by recombinant DNA technology. KOGENATE is intended for use in therapy of classical hemophilia (hemophilia A). KOGENATE is produced by Baby Hamster Kidney (BHK) cells into which the human factor VIII (FVIII) gene has been introduced.<sup>1</sup> KOGENATE 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. In addition to the use of the classical purification methods of ion exchange chromatography and size exclusion chromatography, monoclonal antibody immunoaffinity chromatography is utilized along with other steps designed to purify recombinant factor VIII (rAHF) and remove contaminating substances. The final preparation is stabilized with Albumin (Human) and lyophilized. The concentration of KOGENATE is approximately 100 IU/mL. The product contains no preservatives.

Each vial of KOGENATE contains the labeled amount of rAHF in international units (IU). One IU, as defined by the World Health Organization standard for blood coagulation factor VIII, human, is approximately equal to the level of factor VIII activity found in 1.0 mL of fresh pooled human plasma. The final product when reconstituted as directed contains the following excipients: 10–30 mg glycine/mL, not more than (NMT) 500 µg imidazole/1000 IU, NMT 600 µg polysorbate 80/1000 IU, 2–5 mM calcium chloride, 100–130 mEq/L sodium, 100–130 mEq/L chloride, and 4–10 mg Albumin (Human)/mL. KOGENATE must be administered by the intravenous route.

### CLINICAL PHARMACOLOGY

The clinical trial of KOGENATE has included 168 patients, enrolled over a 55-month period. A total of 16,186 infusions have been utilized in this trial. The study was conducted in several stages.

Initial pharmacokinetic studies were conducted in 17 asymptomatic hemophilic patients, comparing pharmacokinetics of plasma-derived Antihemophilic Factor (Human) (pdAHF) and KOGENATE.<sup>2</sup> The mean biologic half-life of rAHF was 15.8 hours. The mean biologic half-life of pdAHF in the same individuals was 13.9 hours. A similar degree of shortening of the activated partial thromboplastin time was seen with both rAHF and pdAHF. The mean in vivo recovery of rAHF was similar to pdAHF, with a linear dose-response relationship. The recovery and half-life of rAHF was consistent with initial results following 13 weeks of exclusive treatment with Antihemophilic Factor (Recombinant), KOGENATE®. Subsequently, 826 recovery studies were conducted in 58 hemophilic patients participating in later clinical studies. Mean recovery from this group was 2.48% per IU/kg infused.

Fourteen (14) subjects from initial pharmacokinetic studies commenced home treatment with rAHF. Forty-four (44) additional subjects were then enrolled who treated themselves at home exclusively with rAHF. A total of 12,730 infusions have been administered under this portion of the study, of which 1,021 were given in clinic for recovery studies, 7,339 were given for treatment of bleeds, 4,361 were given as prophylaxis, 5 for minor surgery not requiring hospitalization, and 4 for unspecified reason.

Forty-eight (48) patients have received rAHF on 63 occasions for surgical procedures or in-hospital treatment of serious hemorrhage. Eleven (11) received rAHF for the first time in this study, while 37 were already on study or study participants under an investigation of previously untreated patients. Hemostasis has been satisfactory in all cases, with no adverse reactions.

In a study of previously untreated patients, a total of 3,254 infusions have been administered to 96 patients over a 48-month enrollment period. Hemostasis was successfully achieved in all cases.

During the analytical characterization of KOGENATE, analyses for carbohydrate structure revealed the presence of terminal galactose  $\alpha$ 1→3 galactose residues. Since naturally occurring antibody to this structure has been reported in humans, a trial in 18 patients was performed in which the half-life and recovery of rAHF with high levels of this carbohydrate residue was compared to that with KOGENATE, which contains low levels

of this structure. As in the normal population, all patients had preexisting endogenous antibody to galactose  $\alpha 1 \rightarrow 3$  galactose in titers ranging from 1:320 to 1:5120 and no significant change in antibody level was noted during the study. While the mean recovery for KOGENATE in the study, 2.76%/IU/kg (n=43), was significantly different from that of rAHF with high levels of residues, 2.43%/IU/kg (n=155; p=0.0001), the recovery for rAHF with high levels of galactose  $\alpha 1 \rightarrow 3$  galactose is not significantly different from the 2.48%/IU/kg recovery obtained in the larger study from the 58 patients treated with KOGENATE mentioned above. Based on these results, the galactose  $\alpha 1 \rightarrow 3$  galactose residue appears to have no clinical significance.

### **INDICATIONS AND USAGE**

KOGENATE 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. KOGENATE provides a means of temporarily replacing the missing clotting factor in order to correct or prevent bleeding episodes, or in order to perform emergency and elective surgery in hemophiliacs.

KOGENATE can also be used for treatment of hemophilia A in certain patients with inhibitors to factor VIII. In clinical studies of KOGENATE, 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 factor VIII is variable. The dosage can be determined only by clinical response, and by monitoring of circulating factor VIII levels after treatment (see **DOSAGE AND ADMINISTRATION**).

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

### **CONTRAINDICATIONS**

Due to the fact that Antihemophilic Factor (Recombinant), KOGENATE® contains trace amounts of mouse protein (maximum 0.03 ng/IU rAHF) and hamster protein (maximum 0.04 ng/IU rAHF), KOGENATE should be administered with caution to individuals with previous hypersensitivity to pdAHF or known hypersensitivity to biologic preparations with trace amounts of murine or hamster proteins.

Assays to detect seroconversion to mouse and hamster protein were conducted on all patients on study. No patient has developed specific antibody titers against these proteins after commencing study, and no allergic reactions have been associated with rAHF infusions. Although no reactions were observed, patients should be warned of the theoretical possibility of a hypersensitivity reaction, and alerted to the early signs of such a reaction (e.g., hives, generalized urticaria, wheezing and hypotension). Patients should be advised to discontinue use of the product and contact their physician if such symptoms occur.

### **WARNINGS**

None.

### **PRECAUTIONS**

#### **General**

KOGENATE is intended for the treatment of bleeding disorders arising from a deficiency in factor VIII. This deficiency should be proven prior to administering KOGENATE.

The development of circulating neutralizing antibodies to factor VIII may occur during the treatment of patients with hemophilia A. In a study of previously untreated patients, inhibitor antibodies have developed in 17 of the 92 patients (18.5%) who have had at least one follow-up titer. The incidence of antibodies is 15/56 (26.7%) in patients with severe disease (<2% factor VIII), 2/18 (11%) in patients with moderate disease (2–5% factor VIII) and 0/18 in patients with mild disease (>5% factor VIII). Ten of the antibodies were high titer (>10 Bethesda Units), three were low titer, and four were low titer and transient. Studies most closely resembling the design of the study of inhibitor development with KOGENATE have reported incidences of inhibitor formation ranging between 18.4 and 52% for patients treated with pdAHF.<sup>3-6</sup> The incidence of inhibitor formation in previously untreated patients treated with KOGENATE appears to be consistent with that reported in the literature, however the true immunogenicity of KOGENATE is not known at present. Patients treated with rAHF should be carefully monitored for the development of antibodies to rAHF by appropriate clinical observation and laboratory tests.

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 virus including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.

Place needles in sharps container after single use. Discard all equipment including any reconstituted KOGENATE product in accordance with biohazard procedures.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

### **Pediatric Use**

Antihemophilic Factor (Recombinant), KOGENATE® has been proven to be safe and efficacious in newborns and children while under investigation as previously treated (n=21) and previously untreated patients (n=96) (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

### **Pregnancy Category C**

Animal reproduction studies have not been conducted with KOGENATE. It is also not known whether KOGENATE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. KOGENATE should be given to a pregnant woman only if clearly needed.

### **ADVERSE REACTIONS**

During the clinical studies conducted in previously treated patients, 47 out of 12,932 infusions (0.36%) were associated with 58 reported minor adverse reactions. Of these, 19 reactions were local to the injection site (e.g., burning, pruritus, erythema); and 39 were systemic complaints (dizziness, nausea, chest discomfort, sore throat, cold feet, unusual taste in mouth, and slight decrease in blood pressure). In the study with previously untreated patients, 3,254 infusions have been associated with 11 minor adverse reactions (0.34%): two reports of erythema at the injection site, one of facial flushing related to the infusion, one report of diarrhea, two reports of nonspecific rash, two reports of fever, and three reports of emesis. No serious reactions have been reported, and all reactions have been self-limited.

### **DOSAGE AND ADMINISTRATION**

Each bottle of KOGENATE has the rAHF content in international units per bottle stated on the label of the bottle. The reconstituted product must be administered intravenously by either direct syringe injection or drip infusion. The product must be administered within 3 hours after reconstitution.

### **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 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 factor VIII level desired. It is often critical to follow the course of therapy with factor VIII level assays.

The clinical effect of KOGENATE is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more KOGENATE than would be estimated in order to attain satisfactory clinical results. If the calculated dose fails to attain the expected factor VIII 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 rAHF 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 factor VIII without a resultant anamnestic rise in inhibitor titer.<sup>7</sup> Factor VIII 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) or Anti-Inhibitor Coagulant Complex, may be necessary for patients with anamnestic responses to factor VIII treatment and/or high titer inhibitors.

**Calculation of Dosage**

The in vivo percent elevation in factor VIII level can be estimated by multiplying the dose of rAHF per kilogram of body weight (IU/kg) by 2%. This method of calculation is based on clinical findings by Abildgaard et al,<sup>8</sup> and is illustrated in the following examples:

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

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

or

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

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

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

**Mild Hemorrhage**

Mild superficial or early hemorrhages may respond to a single dose of 10 IU per kg,<sup>9</sup> leading to an in vivo rise of approximately 20% in the factor VIII level. Therapy need not be repeated unless there is evidence of further bleeding.

**Moderate Hemorrhage**

For more serious bleeding episodes (e.g., definite hemarthroses, known trauma), the factor VIII level should be raised to 30–50% by administering approximately 15–25 IU per kg. If further therapy is required, a repeat infusion can be given at 12–24 hours.<sup>10</sup>

**Severe Hemorrhage**

In patients with life-threatening bleeding or possible hemorrhage involving vital structures (e.g., central nervous system, retropharyngeal and retroperitoneal spaces, iliopsoas sheath), the factor VIII level should be raised to 80–100% of normal in order to achieve hemostasis. This may be achieved with an initial rAHF (Antihemophilic Factor (Recombinant), KOGENATE®) dose of 40–50 IU per kg and a maintenance dose of 20–25 IU per kg every 8–12 hours.<sup>11,12</sup>

**Surgery**

For major surgical procedures, the factor VIII level should be raised to approximately 100% by giving a preoperative dose of 50 IU/kg. The factor VIII level should be checked to assure that the expected level is achieved before the patient goes to surgery. In order to maintain hemostatic levels, repeat infusions may be necessary every 6 to 12 hours initially, and for a total of 10 to 14 days until healing is complete. The intensity of factor VIII replacement therapy required depends on the type of surgery and postoperative regimen employed. For minor surgical procedures, less intensive treatment schedules may provide adequate hemostasis.<sup>11,12</sup>

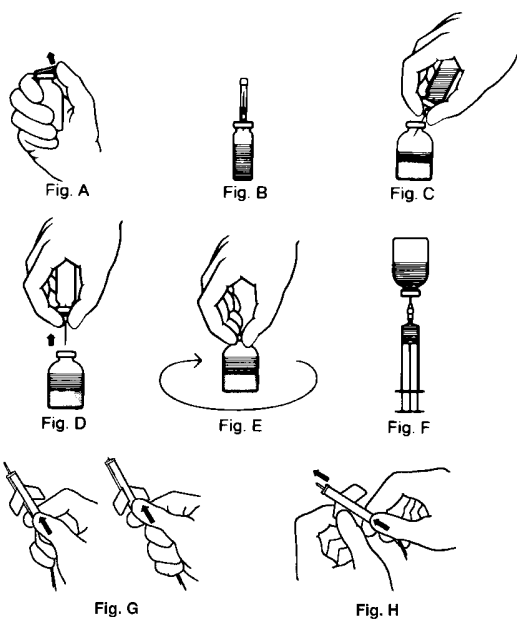
**Prophylaxis**

Factor VIII concentrates may also be administered on a regular schedule for prophylaxis of bleeding, as reported by Nilsson et al.<sup>13</sup>

**Reconstitution****Vacuum Transfer**

1. Warm the unopened diluent and the concentrate to room temperature (NMT 37°C, 99°F).
2. After removing the plastic flip-top caps (Fig. A), aseptically cleanse the rubber stoppers of both bottles.
3. Remove the protective cover from the plastic transfer needle cartridge with tamper-proof seal and penetrate the stopper of the diluent bottle (Fig. B).

4. Remove the remaining portion of the plastic cartridge, invert the diluent bottle and penetrate the rubber seal on the concentrate bottle (Fig. C) with the needle at an angle.  
Alternate method of transferring sterile water: With a sterile needle and syringe, withdraw the appropriate volume of diluent and transfer to the bottle of lyophilized concentrate.
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.
6. After removing the diluent bottle and transfer needle (Fig. D), swirl continuously until completely dissolved (Fig. E).
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: Firmly grasp one or both wings to perform venipuncture; do not use the post-use needle shield for this purpose.



8. After infusion, lock post-use needle shield in place using one of the following methods:
  - a. One-hand technique: Hold tubing in hand and advance needle shield with thumb and index finger until locked over needle tip (Fig. G).
  - b. Two-hand technique: Hold wing stationary and slide needle shield forward with other hand until locked over needle tip (Fig. H).
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.

### 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.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

### HOW SUPPLIED

Antihemophilic Factor (Recombinant), KOGENATE® is supplied in the following single use bottles with the total units of factor VIII activity stated on the label of each bottle. 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 Factor VIII		Diluent
	Activity		
0026-0670-20	250 IU		2.5 mL
0026-0670-30	500 IU		5 mL
0026-0670-50	1000 IU		10 mL

**STORAGE**

KOGENATE 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 without loss of factor VIII activity. Freezing should be avoided, as breakage of the diluent bottle might occur. Do not use beyond the expiration date indicated on the bottle.

**CAUTION**

U.S. federal law prohibits dispensing without prescription.

**LIMITED WARRANTY**

A number of factors beyond our control could reduce the efficacy of this product or even result in an ill effect following its use. These include improper storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biological differences in individual patients. Because of these factors, it is important that this product be stored properly, and that the directions be followed carefully during use. No warranty, express or implied, including any warranty of merchantability or fitness is made. Representatives of the Company are not authorized to vary the terms or the contents of the printed labeling, including the package insert for this product, except by printed notice from the Company's headquarters. The prescriber and user of this product must accept the terms hereof.

**REFERENCES**

1. Lawn RM, Vehar GA: The molecular genetics of hemophilia. *Sci Am* 254(3):48–54, 1986.
2. Schwartz RS, Abildgaard CF, Aledort LM, et al: Human recombinant DNA-derived antihemophilic factor (factor VIII) in the treatment of hemophilia A. *N Engl J Med* 323(26):1800–5, 1990.
3. Lusher JM: Viral safety and inhibitor development associated with monoclonal antibody-purified FVIIIc. *Ann Hematol* 63(3):138–41, 1991.
4. Addiego JE Jr, Gomperts E, Liu S-L, et al: Treatment of hemophilia A with a highly purified factor VIII concentrate prepared by anti-FVIIIc immunoaffinity chromatography. *Thromb Haemost* 67(1):19–27, 1992.
5. Schwarzingler I, Pabinger I, Korninger C, et al: Incidence of inhibitors in patients with severe and moderate hemophilia A treated with factor VIII concentrates. *Am J Hematol* 24(3):241–5, 1987.
6. Ehrenforth S, Kreuz W, Scharrer I, et al: Incidence of development of factor VIII and factor IX inhibitors in hemophiliacs. *Lancet* 339(8793):594–8, 1992.
7. Kasper CK: Complications of hemophilia A treatment: factor VIII inhibitors. *Ann NY Acad Sci* 614:97–105, 1991.
8. Abildgaard CF, Simone JV, Corrigan JJ, et al: Treatment of hemophilia with glycine-precipitated Factor VIII. *N Engl J Med* 275(9):471–5, 1966.
9. Britton M, Harrison J, Abildgaard CF: Early treatment of hemophilic hemarthroses with minimal dose of new factor VIII concentrate. *J Pediatr* 85(2):245–7, 1974.
10. Abildgaard CF: Current concepts in the management of hemophilia. *Semin Hematol* 12(3):223–32, 1975.
11. Hilgartner MW: Factor replacement therapy. In: Hilgartner MW, Pochedly C, eds.: Hemophilia in the child and adult. New York, Raven Press, 1989, pp 1–26.
12. Kasper CK, Dietrich SL: Comprehensive management of haemophilia. *Clin Haematol* 14(2):489–512, 1985.
13. Nilsson IM, Berntorp E, Löfqvist T, et al: Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med* 232(1):25–32, 1992.

**Bayer Corporation**

Pharmaceutical Division  
Elkhart, IN 46515 USA  
U.S. License No. 8

14-7670-007  
(Rev. Oct. 1998)