

**PRODUCT MONOGRAPH**

**RECOMBINATE  
ANTIHEMOPHILIC FACTOR (RECOMBINANT)  
RECOMBINATE for Injection**

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**PREPARATION DATE:  
December 9, 2004**

**Control#: 081898**

**RECOMBINATE**  
**Antihemophilic Factor (Recombinant)**  
**RECOMBINATE for Injection**

**DESCRIPTION**

RECOMBINATE, Antihemophilic Factor (Recombinant) (rAHF) is a glycoprotein synthesized by a genetically engineered Chinese Hamster Ovary (CHO) cell line. In culture, the CHO cell line secretes recombinant antihemophilic factor (rAHF) into the cell culture medium. The rAHF is purified from the culture medium utilizing a series of chromatography columns. A key step in the purification process is an immunoaffinity chromatography methodology in which a purification matrix, prepared by immobilization of a monoclonal antibody directed to factor VIII, is utilized to selectively isolate the rAHF in the medium. The synthesized rAHF produced by the CHO cells has the same biological effects as Antihemophilic Factor (Human) [AHF (Human)]. Structurally the protein has a similar combination of heterogenous heavy and light chains as found in AHF (Human).

RECOMBINATE rAHF is formulated as a sterile, nonpyrogenic, off-white to faint yellow, lyophilized powder preparation of concentrated recombinant AHF for intravenous injection. RECOMBINATE rAHF is available in single-dose bottles which contain nominally 250, 500 and 1000 International Units per bottle. When reconstituted with the appropriate volume of diluent, the product contains the following stabilizers in maximum amounts: 12.5 mg/mL Albumin (Human), 0.20 mg/mL calcium, 1.5 mg/mL polyethylene glycol (3350), 180 mEq/L sodium, 55 mM histidine, 1.5 µg/AHF International Unit (IU) polysorbate-80. Von Willebrand Factor (vWF) is coexpressed with the Antihemophilic Factor (Recombinant) and helps to stabilize it. The final product contains not more than 2 ng vWF/IU rAHF which will not have any clinically relevant effect in patients with von Willebrand's disease. The product contains no preservative.

Manufacturing of RECOMBINATE rAHF is shared by Baxter Healthcare Corporation and Genetics Institute, Inc. The recombinant Antihemophilic Factor Concentrate (For Further Manufacturing Use), is produced by Baxter Healthcare Corporation and Genetics Institute (For Further Manufacturing Use) and subsequently formulated and packaged at Baxter Healthcare Corporation.

Each bottle of RECOMBINATE rAHF is labeled with the AHF activity expressed in IU per bottle. Biological potency is determined by an *in vitro* assay which is referenced to the World Health Organization (WHO) International Standard for Factor VIII:C Concentrate.

**CLINICAL PHARMACOLOGY**

AHF is the specific clotting factor deficient in patients with hemophilia A (classical hemophilia). Hemophilia A is a genetic bleeding disorder characterized by hemorrhages which may occur spontaneously or after minor trauma. The administration of RECOMBINATE rAHF provides an increase in plasma levels of AHF and can temporarily correct the coagulation defect in these patients. Pharmacokinetic studies on sixty-nine (69) patients revealed the circulating mean half-life for rAHF to be  $14.6 \pm 4.9$  hours (n=67), which was not statistically significantly different

from plasma-derived HEMOFIL M, Antihemophilic Factor (Human) (AHF) (pdAHF). The mean half-life of HEMOFIL M AHF was  $14.7 \pm 5.1$  hours (n=61). The actual baseline recovery observed with rAHF was  $123.9 \pm 47.7$  IU/dL (n=23) which is significantly higher than the actual HEMOFIL M AHF baseline recovery of  $101.7 \pm 31.6$  IU/dL (n=61). However, the calculated ratio of actual to expected recovery with rAHF ( $121.2 \pm 48.9\%$ ) is not different on average from HEMOFIL M AHF ( $123.4 \pm 16.4\%$ ).

The clinical study of rAHF in previously treated patients (individuals with hemophilia A who had been treated with plasma derived AHF) was based on observations made on a study group of 69 patients. These individuals received cumulative amounts of Factor VIII ranging from 20,914 to 1,383,063 IU over the 48 month study. Patients were given a total of 17,700 infusions totaling 28,090,769 IU rAHF.

These patients were successfully treated for bleeding episodes on a demand basis and also for the prevention of bleeds (prophylaxis). Spontaneous bleeding episodes successfully managed include hemarthroses, soft tissue and muscle bleeds. Management of hemostasis was also evaluated in surgeries. A total of 24 procedures on 13 patients were performed during this study. These included minor (e.g. tooth extraction) and major (e.g. bilateral osteotomies, thoracotomy and liver transplant) procedures. Hemostasis was maintained perioperatively and postoperatively with individualized AHF replacement.

A study of rAHF in previously untreated patients was also performed as part of an ongoing study. The study group was comprised of seventy-nine (79) patients, of whom seventy-six (76) had received at least one infusion of rAHF. To date, this cohort has been given 12,209 infusions totaling over 11,277,043 IU rAHF. Hemostasis was appropriately managed in spontaneous bleeding episodes, intracranial hemorrhage and surgical procedures.

## **INDICATIONS AND USAGE**

The use of RECOMBINATE rAHF is indicated in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes<sup>1</sup>. RECOMBINATE rAHF is also indicated in the perioperative management of patients with hemophilia A (classical hemophilia).

RECOMBINATE rAHF can be of therapeutic value in patients with acquired AHF inhibitors not exceeding 10 Bethesda Units per mL<sup>2</sup>. In clinical studies with RECOMBINATE rAHF, patients with inhibitors who were entered into the previously treated patient trial and those previously untreated children who have developed inhibitor activity on study, showed clinical hemostatic response when the titer of inhibitor was less than 10 Bethesda Units per mL. In such uses, however, the dosage of RECOMBINATE rAHF should be controlled by frequent laboratory determinations of circulating AHF levels.

RECOMBINATE rAHF is not indicated in von Willebrand's disease.

## **CONTRAINDICATIONS**

Known hypersensitivity to mouse, hamster or bovine protein may be a contraindication to the use of Antihemophilic Factor (Recombinant) (see **Precautions**).

## **WARNINGS**

None.

## **PRECAUTIONS**

### **General**

Certain components used in the packaging of this product contain natural rubber latex.

**Identification of the clotting defect as a Factor VIII deficiency is essential before the administration of RECOMBINATE, Antihemophilic Factor (Recombinant) (rAHF) is initiated.** No benefit may be expected from this product in treating other deficiencies.

The formation of neutralizing antibodies, inhibitors to factor VIII, is a known complication in the management of individuals with hemophilia A. The reported prevalence of these antibodies in patients receiving plasma derived AHF is 10-20%<sup>3-7, 10-12</sup>. These inhibitors are invariably IgG immunoglobulins, the factor VIII procoagulant inhibitory activity of which is expressed as Bethesda Units (B.U.) per mL of plasma or serum<sup>3-7</sup>. Over the investigational period, none of the 69 previously treated individuals, without an inhibitor at entry into the study, developed an inhibitor. In the previously untreated patient group there were 76 eligible patients with factor VIII levels less than or equal to 2% who were tested for inhibitor after treatment with RECOMBINATE rAHF. Of this group, 23 individuals developed detectable inhibitor and of these, 8 patients showed a titer greater than 10 B.U. Patients treated with rAHF should be carefully monitored for the development of antibodies to rAHF by appropriate clinical observations and laboratory tests.

### **Formation of Antibodies to Mouse, Hamster or Bovine Protein**

As RECOMBINATE rAHF contains trace amounts of mouse protein (maximum of 0.1 ng/IU rAHF), hamster protein (maximum of 1.5 ng CHO protein/IU rAHF), and bovine protein (maximum of 1 ng BSA/IU rAHF), the remote possibility exists that patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

### **Information for Patients**

The patient and physician should discuss the risks and benefits of this product.

Although allergic type hypersensitivity reactions were not observed in any patient receiving RECOMBINATE rAHF on study, such reactions are theoretically possible. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician if these symptoms occur.

### **Laboratory Tests**

Although dosage can be estimated by the calculations which follow, it is strongly recommended that whenever possible, appropriate laboratory tests be performed on the patient's plasma at suitable intervals to assure that adequate AHF levels have been reached and are maintained.

If the patient's plasma AHF fails to reach expected levels or if bleeding is not controlled after adequate dosage, the presence of inhibitor should be suspected. By performing appropriate laboratory procedures, the presence of an inhibitor can be demonstrated and quantified in terms of AHF International Units neutralized by each mL of plasma or by the total estimated plasma volume. If the inhibitor is present at levels less than 10 Bethesda Units per mL, administration of additional AHF may neutralize the inhibitor. Thereafter, the administration of additional AHF International Units should elicit the predicted response. The control of AHF levels by laboratory assay is necessary in this situation.

Inhibitor titers above 10 Bethesda Units per mL may make hemostasis control with AHF either impossible or impractical because of the very large dose required. In addition, the inhibitor titer may rise following AHF infusion because of an anamnestic response to the AHF antigen.

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

RECOMBINATE, Antihemophilic Factor (Recombinant) (rAHF) was tested for mutagenicity at doses considerably exceeding plasma concentrations of rAHF *in vitro* and at doses up to ten times the expected maximum clinical dose *in vivo*, RECOMBINATE rAHF did not cause reverse mutations, chromosomal aberrations, or an increase in micronuclei in bone marrow polychromatic erythrocytes. Long term studies in animals have not been performed to evaluate carcinogenic potential.

#### **Pediatric Use**

RECOMBINATE rAHF is appropriate for use in children of all ages, including the newborn. Safety and efficacy studies have been performed in both previously treated (n=23) and previously untreated (n=76) children. (See **Clinical Pharmacology** and **Precautions**).

#### **Pregnancy**

Pregnancy Category C. Animal reproduction studies have not been conducted with Antihemophilic Factor (Recombinant). It is not known whether Antihemophilic Factor (Recombinant) can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Antihemophilic Factor (Recombinant) should be given to a pregnant woman only if clearly needed.

### **ADVERSE REACTIONS**

During the clinical studies conducted in the previously treated patient group, there were 13 infusion related minor adverse reactions reported out of 10,446 infusions (0.12%). One patient experienced flushing and nausea during his first infusion which abated on decreasing the infusion rate. A second patient experienced mild fatigue during and following one infusion and a third patient had a series of eleven nose bleeds with a periodicity associated with the infusions.

The protein in greatest concentration in RECOMBINATE rAHF is Albumin (Human). Reactions associated with intravenous administration of albumin are extremely rare, although nausea,

fever, chills or urticaria have been reported. Other allergic reactions could theoretically be encountered in the use of this Antihemophilic Factor preparation. See **Information for Patients**.

## DOSAGE AND ADMINISTRATION

Each bottle of RECOMBINATE rAHF is labeled with the AHF activity expressed in IU per bottle. This potency assignment is referenced to the World Health Organization International Standard for Factor VIII:C Concentrate and is evaluated by appropriate methodology to ensure accuracy of the results.

The expected *in vivo* peak increase in AHF level expressed as IU/dL of plasma or % (percent) of normal can be estimated by multiplying the dose administered per kg body weight (IU/kg) by two. This calculation is based on the clinical findings of Abildgaard et al<sup>8</sup> and is supported by the data generated by 419 clinical pharmacokinetic studies with rAHF in 67 patients over time. This pharmacokinetic data demonstrated a peak recovery point above the pre-infusion baseline of approximately 2.0 IU/dL per IU/kg body weight.

Example (Assuming patient's baseline AHF level is at <1%):

- (1) A dose of 1750 IU AHF administered to a 70 kg patient, *i.e.* 25 IU/kg (1750/70), should be expected to cause a peak post-infusion AHF increase of  $25 \times 2 = 50$  IU/dL (50% of normal).
- (2) A peak level of 70% is required in a 40 kg child. In this situation the dose would be  $70/2 \times 40 = 1400$  IU.

### Recommended Dosage Schedule

Physician supervision of the dosage is required. The following dosage schedule may be used as a guide.

<b>Hemorrhage</b>		
<b>Degree of hemorrhage</b>	<b>Required peak post-infusion AHF activity in the blood (as % of normal or IU/dL plasma)</b>	<b>Frequency of infusion</b>
Early hemarthrosis or muscle bleed or oral bleed	20-40	Begin infusion every 12 to 24 hours for one-three days until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive hemarthrosis, muscle bleed, or hematoma	30-60	Repeat infusion every 12 to 24 hours for usually three days or more until pain and disability are resolved.
Life threatening bleeds such as head injury, throat bleed, severe abdominal pain	60-100	Repeat infusion every 8 to 24 hours until threat is resolved.

Surgery		
Type of operation		
Minor surgery, including tooth extraction	60-80	A single infusion plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases.
Major surgery	80-100 (pre- and post-operative)	Repeat infusion every 8 to 24 hours depending on state of healing.

The careful control of the substitution therapy is especially important in cases of major surgery or life threatening hemorrhages. Although dosage can be estimated by the calculations above, it is strongly recommended that whenever possible, appropriate laboratory tests including serial AHF assays be performed on the patient's plasma at suitable intervals to assure that adequate AHF levels have been reached and are maintained.

Other dosage regimens have been proposed such as that of Schimpf, *et al*, which describes continuous maintenance therapy.<sup>9</sup>

#### Reconstitution: Use Aseptic Technique

1. Bring RECOMBINATE, Antihemophilic Factor (Recombinant) (rAHF) (dry concentrate) and Sterile Water for Injection, USP, (diluent) to room temperature.
2. Remove caps from both the diluent and concentrate bottles to expose the rubber stoppers.
3. Disinfect the stoppers with an alcohol swab or other suitable solution suggested by your doctor or hemophilia treatment centre.
4. Open the device package by peeling away the lid without touching the inside of the package. The BAXJECT device remains in the package at this time (Fig. a).
5. Turn the package, with the device, upside down, and place over the top of the diluent bottle.
6. Insert the spike of the BAXJECT device into the centre of the diluent bottle's stopper by pushing down (Fig. b).
7. Grip the package at its edge and pull it off the device. Do not touch the exposed spike (Fig. b).
8. Quickly turn over the diluent bottle with the BAXJECT device, place on top of the bottle containing the concentrate.
9. Insert the spike into the concentrate bottle's stopper (Fig. c). The vacuum will draw the diluent into the concentrate bottle.
10. Swirl the concentrate solution gently until it is completely dissolved. **Do not shake.**



NOTE: Do not refrigerate after reconstitution. See **Administration**.

#### Administration: Use Aseptic Technique

Administer at room temperature.

RECOMBINATE rAHF should be administered not more than 3 hours after reconstitution.

### Intravenous Syringe Injection

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. A colorless to faint yellow appearance is acceptable for RECOMBINATE rAHF.

Plastic Luer lock syringes are recommended for use with this product since proteins such as AHF tend to stick to the surface of all-glass syringes.

1. **Turn the handle down**, towards the concentrate solution bottle, until it snaps into position (Fig. d[1]).
2. Remove the cap from the BAXJECT device (Fig. d[2]).
3. Choose a Luer Lock syringe. If the syringe has a tip protector cap, remove it now.
4. Pull back the plunger to the amount of concentrate solution that will be withdrawn (Fig. e[1]).
5. With the concentrate solution bottle on the bottom, ensure that the device handle is pointing downwards.
6. Securely connect the syringe by twisting it onto the syringe connection of the BAXJECT device and inject the air into the concentrate solution bottle (Fig. e[2]).
7. While keeping the syringe plunger in place, turn the system over so that the concentrate solution bottle is on top.
8. Withdraw the concentrate solution into the syringe by pulling the plunger slowly (Fig. f).
9. Return the handle to the middle position, facing away from both bottles, and disconnect the syringe.
10. Leave the BAXJECT system connected. Dispose of the BAXJECT system as recommended by your healthcare professional.



### Rate of Administration

Preparations of RECOMBINATE, Antihemophilic Factor (Recombinant) (rAHF) can be administered at a rate of up to 10 mL per minute with no significant reactions.

The pulse rate should be determined before and during administration of RECOMBINATE rAHF. Should a significant increase in pulse rate occur, reducing the rate of administration or temporarily halting the injection usually allows the symptoms to disappear promptly.

### HOW SUPPLIED



RECOMBINATE rAHF is available in single-dose bottles which contain nominally 250, 500 and 1000 International Units per bottle. RECOMBINATE rAHF is packaged with 10 mL of Sterile Water for Injection, USP, a BAXJECT needleless transfer device, and one package insert.

## STORAGE

RECOMBINATE rAHF can be stored under refrigeration [2 °C – 8 °C (36 °F – 46 °F)] or at room temperature, not to exceed 30 °C (86 °F). Avoid freezing to prevent damage to the diluent bottle. Do not use beyond the expiration date printed on the box.

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