

RECOMBINATE™

Octocog alfa [rAHF, Factor VIII (rch)]

DESCRIPTION

RECOMBINATE is a sterile, non-pyrogenic, off-white to faint yellow lyophilised powder preparation of concentrated recombinant Antihæmophilic Factor (rAHF) for intravenous injection and is available in single dose vials containing 250, 500 and 1000IU nominally per vial. When reconstituted with the appropriate volume of diluent (10mL) each vial contains the following excipients in maximum amounts: 125mg Albumin (Human), 15mg Macrogol 3350, 105mg Sodium Chloride, 85mg Histidine, and 7.3mg Calcium Chloride. Polysorbate 80 (1.5µg/AHF IU, ie., 1.5mg in **RECOMBINATE** 1000IU, 0.750mg in 500IU and 0.375mg in 250IU presentations) is present as an impurity of the manufacturing process.

The active ingredient in **RECOMBINATE**, octocog alfa [rAHF, Factor VIII (rch)], is a glycoprotein synthesized using genetically engineered Chinese Hamster Ovary (CHO) cells. The CHO cells secrete rAHF into a cell culture medium, which is then purified by a series of chromatography columns. The rAHF is selectively isolated in a purification matrix prepared by immobilisation of a monoclonal antibody directed to Factor VIII. The rAHF produced has the same biological effects as natural human Antihæmophilic Factor (AHF). The von Willebrand Factor (vWF) is co-expressed with the rAHF and helps to stabilize it.

PHARMACOLOGY

General

Under normal physiological condition, factor VIII is essential for blood clotting and hæmostatis. The activated factor VIII (FVIIIa) acts as cofactor for activating factor IX to FIXa, cascading to activate factor X to FXa. By the actions of the activated factors Va and Xa, the circulating prothrombin is converted into thrombin. Subsequently, thrombin converts fibrinogen to fibrin monomer cascading to formation of linear fibrin polymer. By the action of factor XIII the fibrin monomer is cross-linked to form fibrin clots leading to the arrest of the bleeding episodes.

In patients with hæmophilia A (classical hæmophilia), a sex-linked hereditary disorder of blood coagulation, the levels of circulating factor VIII is decreased, leading to profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. The use of plasma-derived or recombinant derived factor VIII has been shown successfully to correct this deficiency. Thus, the plasma derived and recombinant derived factor VIII has the same pharmacological actions.

CLINICAL TRIAL

Pharmacokinetic studies on sixty-nine (69) patients revealed the circulating mean half-life of rAHF to be 14.6 ± 4.9 hours ($n = 67$), which was not significantly different statistically from Baxter Healthcare Corporation's plasma-derived Antihemophilic Factor (Human) (pdAHF). The mean half-life of pdAHF was 14.7 ± 5.1 hours ($n = 61$). The actual baseline recovery observed with rAHF was 123.9 ± 47.7 IU/dL ($n = 23$), which is significantly higher than the actual pdAHF baseline recovery of 101.7 ± 31.6 IU/dL ($n = 61$). However, the calculated ratio of actual to expected recovery with rAHF ($121.2 \pm 48.9\%$) is similar to that of pdAHF ($123.4 \pm 16.4\%$).

The clinical study of rAHF in previously treated patients involved observations made on a study group of 69 patients. These individuals received 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. Spontaneous bleeding episodes successfully managed include haemarthroses, soft tissue and muscle bleeds. Management of haemostasis in surgical procedures was also evaluated. A total of 24 procedures on 13 patients were performed during this study. These included minor (e.g. tooth extraction) and major (e.g. liver transplant, thoracotomy, bilateral osteotomies). Haemostasis was maintained perioperatively and postoperatively with individualised AHF replacement.

A study of rAHF in previously untreated patients was also performed. The study group comprised seventy-nine (79) patients of whom seventy-six (76) had received at least one infusion of rAHF. In total, this group has been given 12,209 infusions totalling 11,277,043 IU rAHF. Haemostasis was appropriately managed in spontaneous bleeding episodes, intracranial haemorrhage and surgical procedures.

INDICATIONS

The use of **RECOMBINATE** [Antihemophilic Factor (Recombinant)] is indicated in haemophilia A (classical haemophilia) for the prevention and control of haemorrhagic episodes¹. **RECOMBINATE** is also indicated in the perioperative management of patients with haemophilia A (classical haemophilia).

RECOMBINATE can be of therapeutic value in patients with acquired Factor VIII inhibitors not exceeding 10 Bethesda Units per mL. In clinical studies with **RECOMBINATE**, 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 haemostatic response when the titer of inhibitor was less than 10 Bethesda Units per mL. However, in such uses, the dosage of **RECOMBINATE** should be controlled by frequent laboratory determinations of circulating Factor VIII levels.

RECOMBINATE is not indicated in von Willebrand's disease.

CONTRAINDICATIONS

Known hypersensitivity to the active substance, excipients or to mouse, hamster or bovine protein may be a contraindication to the use of **RECOMBINATE**.

PRECAUTIONS

General

Certain components used in the packaging of this product contain natural rubber latex which may cause allergic reactions.

Allergic type hypersensitivity reactions, including anaphylaxis, have been observed with **RECOMBINATE** and have been manifested by dizziness, rash, flushing, angioedema/face swelling, urticaria, pruritus, loss of consciousness, dyspnoea, hypotension, pallor, pyrexia, paresthesia, and nausea.

Use with caution in the following circumstances

Patients treated with rAHF should be carefully monitored for the development of antibodies to rAHF by appropriate clinical observations and laboratory tests. As this product contains trace amounts of mouse, hamster and bovine protein, the possibility exists that patients treated with **RECOMBINATE** may develop hypersensitivity to these non-human mammalian proteins. The capacity for these proteins to elicit the immunological responses in animals has not been systematically examined.

Check the following before use

Identification of the clotting defect as a Factor VIII deficiency is essential prior to initiation of **RECOMBINATE** treatment. Benefit will not be gained by using this treatment on other clotting defects.

Formation of antibodies to Factor VIII

The formation of neutralising antibodies, inhibitors to Factor VIII, is a known complication in the management of individuals with haemophilia A. The reported prevalence of these antibodies in patients receiving plasma derived AHF is 10 - 20%^{3,4,5,6,7,10,11,12}. 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^{3,4,5,6,7}. Over the investigational period, none of the 65 previously treated individuals, without an inhibitor at entry into the study, developed an inhibitor. In the previously untreated patient group there were 66 patients with Factor VIII levels less than or equal to 2% who were tested for inhibitor after treatment with **RECOMBINATE**, rAHF. Of this group, 12 individuals developed detectable inhibitor, and of these, 3 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.

The risk for inhibitor development depends on a number of factors relating to the characteristics of the patient (e.g., type of the Factor VIII gene mutation, family history, ethnicity), which are believed to represent the most significant risk factors for inhibition formation. Inhibitors have predominantly been reported in previously untreated patients.

Formation of Antibodies to Mouse, Hamster or Bovine Protein

Patients treated with Factor VIII [rAHF, (rch)] may develop hypersensitivity to trace amounts of non-human mammalian proteins present, these being mouse protein (maximum 0.1 nanogram/IU rAHF activity), hamster protein (maximum 1.5 nanogram CHO protein/IU rAHF activity) and bovine protein (maximum 1 nanogram bovine serum albumin/IU rAHF activity).

Carcinogenicity/Mutagenicity

Long term animal studies have not been performed to evaluate carcinogenic potential. Testing for mutagenicity conducted *in vitro* at doses considerably exceeding plasma concentrations of rAHF, and *in vivo* at doses up to ten times the expected maximum clinical dose, did not detect reverse mutations, chromosomal aberrations nor an increase in micronuclei in bone marrow polychromatic erythrocytes.

Impairment of fertility

Animal studies to determine the effect of **RECOMBINATE** on fertility have not been conducted.

Pregnancy and lactating

Pregnancy Category B2. Animal reproduction studies have not been conducted with **RECOMBINATE**. As it is not known whether **RECOMBINATE** can cause foetal harm damage, **RECOMBINATE** should be given to a pregnant woman only if clearly needed. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing **RECOMBINATE**.

Use in lactation

It is not known whether **RECOMBINATE** or its metabolites are excreted in human milk. Nursing is not recommended in women being treated with **RECOMBINATE**. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing **RECOMBINATE**.

Paediatric Use

RECOMBINATE is appropriate for use in children of all ages, including the newborn. Safety and efficacy has been determined in both previously treated and previously untreated children. (See **Precautions.**)

Interactions with other drugs

None known.

Effects on Laboratory Tests

It is recommended that appropriate laboratory testing be performed on each patient's plasma at suitable intervals to ensure the maintenance of adequate AHF levels.

In the case where bleeding is uncontrolled, these laboratory investigations may detect the presence of an inhibitor which can be quantified in terms of AHF IU neutralised by each mL of plasma. If the inhibitor is present at levels less than 10 Bethesda Units per mL, administration of additional AHF may neutralise the inhibitor. Thereafter, the administration of additional AHF should elicit the predicted response. The control of AHF by laboratory assays is necessary in these situations.

Animal toxicity

Repeat dose toxicity studies, with intravenous administration of **RECOMBINATE** to rats and cynomolgus monkeys, have been limited to duration of 4 weeks.

Effects on Ability to Drive and Use Machines

There is no information of the effects of **RECOMBINATE** on the ability to drive or operate an automobile or other heavy machinery.

ADVERSE REACTIONS

Adverse Reactions from Clinical Trials

Adverse reactions to **RECOMBINATE** are rare (less than 1 report per 10⁶ IU used in clinical studies). Adverse reactions reported in clinical studies have included the following:

Gastrointestinal Disorders

Nausea, vomiting

General Disorders and Administration Site Conditions

Chills, fatigue, pyrexia, chest tightness, coughing, diaphoresis

Infections and Infestations

Ear infection

Investigations

Acoustic stimulation tests abnormal

Musculoskeletal and Connective Tissue Disorders

Pain in extremity

Nervous System Disorders

Dizziness, tremor

Respiratory, Thoracic and Mediastinal Disorders

Pharyngolaryngeal pain, dyspnoea (moderate to severe)

Skin and Subcutaneous Tissue Disorders

Hyperhidrosis, pruritus, rash, rash maculopapular, burning sensation, erythema, urticaria, cyanosis

Vascular Disorders

Epistaxis, flushing, haematoma, hypotension, pallor, peripheral coldness

During the PTP (previously treated patients) study, none of the 71 subjects developed *de novo* evidence of Factor VIII inhibitor. However, during the phase II/III portion of the study, 1 subject with a history of inhibitors exhibited inhibitor activity at 6 months (0.8 Bethesda Units [BU]), which resolved by 9 months. One other subject in this study had detectable Factor VIII inhibitor at baseline (1.26BU) and exhibited an anamnestic response at 6 months (10.3BU). During study 039801, none of the 34 treated subjects developed a Factor VIII inhibitor.

During the PUP (previously untreated patients), 22 of the 73 evaluable subjects developed inhibitors to Factor VIII. Of these, 13 subjects displayed no detectable Factor VIII inhibitors at study exit.

The presence of Albumin (Human) in **RECOMBINATE** is associated with the following allergic reactions: nausea, fever, chills and urticaria. Reports of such reactions, however, are extremely rare.

Patients should be advised to discontinue use of **RECOMBINATE** and seek medical advice in the event of any allergic reactions, including: fever spike, hives, generalised urticaria, shortness of breath, tightness of the chest, wheezing, hypotension, and anaphylaxis.

Post-Marketing Adverse Reactions

In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported in the post marketing experience.

Blood and Lymphatic System disorders

Factor VIII inhibition

Cardiac Disorders

Tachycardia, cyanosis

Gastrointestinal Disorders

Vomiting, abdominal pain

General Disorders and Administration Site Conditions

Malaise, Injection site reactions, chest pain, chest discomfort

Immune System Disorders

Anaphylactic reaction, Hypersensitivity

Nervous System Disorders

Loss of consciousness, headache, paresthesia

Respiratory, Thoracic and Mediastinal Disorders

Dyspnoea, cough

Skin and Subcutaneous Tissue Disorders

Angioedema, Urticaria, Erythema

DOSAGE AND ADMINISTRATION

If bleeding is not controlled with the recommended dose, the plasma level of Factor VIII should be determined and a sufficient dose of **RECOMBINATE** should be administered to achieve a satisfactory clinical response. The careful control of the substitution therapy is especially important in cases of major surgery or life threatening haemorrhages. Under certain circumstances (e.g., presence of a low titer inhibitor) doses larger than those recommended may be necessary.

Patients should be evaluated for the development of Factor VIII inhibitors, if the expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose.

Each vial of **RECOMBINATE** is labelled in accordance with the World Health Organisation International Standard for Factor VIII Concentrate with the AHF activity expressed in IU per vial.

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 (2). This calculation is based on clinical findings⁸ and is supported by the data generated over time in 419 clinical pharmacokinetic studies with rAHF in 67 patients.

This 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%):

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

The following table may be used as a guide for physicians:

| Haemorrhage | | |
|--|---|---|
| Degree of haemorrhage | Required peak post-infusion AHF activity in the blood (as % of normal or IU/dL plasma) | Frequency of infusion |
| Early haemarthrosis or muscle bleed or oral bleed | 20 - 40 | Begin infusion every 12 to 24 hours for one to three days until the bleeding episode as indicated by pain is resolved or healing is achieved. |
| More extensive haemarthrosis, muscle bleed, or haematoma | 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. |

If bleeding is not controlled with the prescribed dose, the plasma level of Factor VIII should be determined and a sufficient dose of **RECOMBINATE** should be administered to achieve a satisfactory clinical response. The careful control of the substitution therapy is especially important in cases of major surgery or life-threatening haemorrhages. Under certain circumstances (e.g., presence of a low titer inhibitor) doses larger than those prescribed may be necessary.

Reconstitution: Use Aseptic Technique

1. Bring **RECOMBINATE** (dry concentrate) and Sterile Water for Injection, USP, (diluent) to room temperature.
2. Remove caps from concentrate and diluent vial.
3. Cleanse stoppers with germicidal solution and allow to dry prior to use.
4. Remove protective covering from one end of double-ended needle and insert exposed needle through the centre of the stopper.
5. Remove protective covering from other end of double-ended needle. Invert diluent vial over the upright **RECOMBINATE** vial, then rapidly insert free end of the needle through the **RECOMBINATE** vial stopper at its centre. The vacuum in the vial will draw in the diluent.
6. Disconnect the two vials by removing needle from diluent vial stopper, then remove needle from **RECOMBINATE** vial. Swirl gently until all the material is completely dissolved, otherwise active material will be removed by the filter needle.

Note: Do not refrigerate after reconstitution. (See **Administration.**)

Administration: Use Aseptic Technique

Administer at room temperature. **RECOMBINATE** should be administered not more than 3 hours after reconstitution.

Intravenous Syringe Injection

RECOMBINATE should be inspected for particulate matter and discolouration after reconstitution and prior to administration. A colourless to faint yellow appearance is acceptable for Antihemophilic Factor, **RECOMBINATE**.

Plastic syringes are recommended when administering **RECOMBINATE** as proteins such as AHF tend to stick to the surface of glass syringes.

1. Attach filter needle to a disposable syringe and draw back plunger to admit air into the syringe.
2. Insert the needle into reconstituted **RECOMBINATE**.
3. Inject air into vial and then withdraw the reconstituted material into the syringe.

4. Remove and discard the filter needle from the syringe; attach a suitable needle and inject intravenously as instructed under Rate of Administration.
5. If a patient is to receive more than one vial of **RECOMBINATE**, the contents of multiple vials may be drawn into the same syringe by drawing up each vial through a separate unused filter needle.
Please note: filter needles are intended to filter the contents of a single vial of **RECOMBINATE** only.

Rate of Administration

Preparations of **RECOMBINATE** can be administered at a rate of up to 10mL per minute with no significant reactions and ensuring comfort of the patient. The pulse rate should be determined before and during administration of **RECOMBINATE**. 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.

OVERDOSAGE

No symptoms of overdose are known.

PRESENTATION

Package

RECOMBINATE is available single-dose vials which contain nominally 250, 500 and 1000IU per vial. **RECOMBINATE** is packaged with 10mL of Sterile Water for Injection, USP, a double-ended needle, a filter needle and one package insert.

SHELF LIFE AND STORAGE

RECOMBINATE should be stored under refrigeration [2 - 8°C; do not freeze] or stored below 25°C. Avoid freezing to prevent damage to the diluent vial. Do not use beyond the expiration of the product. Refer to the expiry date printed on the carton box.

MEDICINE CLASSIFICATION

General Sale Medicine.

REFERENCES

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NAME AND ADDRESS OF THE SPONSOR

RECOMBINATE is manufactured by:

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