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 factor VIII (rAHF) for intravenous injection and is available in single dose vials containing 250, 500 and 1000IU (International Units) 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/Factor VIII IU, i.e., 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 [Antihaemophilic Factor (Recombinant)], is a glycoprotein synthesized using genetically engineered Chinese Hamster Ovary Cells (CHO). The CHO cells secrete recombinant Factor VIII (rFVIII) into a cell culture medium, which is then purified by a series of chromatography columns. The rFVIII is selectively isolated in a purification matrix prepared by immobilisation of a monoclonal antibody directed to Factor VIII. The rFVIII produced has the same biological effects as natural human Factor VIII. Recombinant von Willebrand Factor (rVWF) is co-expressed with the rFVIII and helps to stabilize it.

PHARMACOLOGY

General

Under normal physiological condition, Factor VIII is essential for blood clotting and haemostatis. 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 haemophilia A (classical haemophilia), 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 TRIALS

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

The clinical study of RECOMBINATE in previously treated patients involved observations made on a study group of 69 patients. These individuals received from 20,914 to 1,383,063IU over the 48 month study. Patients were given a total of 17,700 infusions totaling 28,090,769IU of RECOMBINATE. 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 Factor VIII replacement.

A study of RECOMBINATE 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 RECOMBINATE. In total, this group has been given 12,209 infusions totaling 11,277,043IU of RECOMBINATE. 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 episodes. 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

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 RECOMBINATE should be carefully monitored for the development of antibodies to Factor VIII 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

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.

The development of neutralising antibodies (inhibitors) to Factor VIII is a known complication in the treatment of patients with Haemophilia A. The reported prevalence of these antibodies in patients receiving plasma derived Factor VIII is 10 - 20%. These inhibitors are invariably IgG immunoglobulins, the Factor VIII procoagulant inhibitory activity of which is expressed as Bethesda Units (BU) per mL of plasma or serum. The risk of developing inhibitors is correlated to the extent of exposure to Factor VIII, the risk being highest within the first 20 exposure days,
and to other genetic and environmental factors. 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 inhibitor formation. Inhibitors have predominantly been reported in previously untreated patients. 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. Of this group, 12 individuals developed detectable inhibitor, and of these, 3 patients showed a titer greater than 10BU. Patients treated with Factor VIII should be carefully monitored for the development of antibodies to Factor VIII by appropriate clinical observations and laboratory tests.

**Formation of antibodies to mouse, hamster or bovine protein**

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

**Effects on fertility**

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

**Use in pregnancy**

Pregnancy Category B2. Animal reproduction studies have not been conducted with RECOMBINATE. As it is not known whether RECOMBINATE can cause foetal 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**.)

**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.

**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 Factor VIII 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 Factor VIII IU neutralised by each mL of plasma. If the inhibitor is present at levels less than 10 BU per mL, administration of additional Factor VIII may neutralise the inhibitor. Thereafter, the administration of additional Factor VIII International Units should elicit the predicted response. The control of Factor VIII 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.

**Interactions with other medicines**

None known. No interaction studies have been performed with RECOMBINATE.

**ADVERSE EFFECTS**

**Adverse effects from clinical trials**

Adverse reactions to RECOMBINATE are rare (less than 1 report per 10^6 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**
Hyperhydrosis, 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 effects

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**

**RECOMBINATE** is intended for intravenous administration, and not for intramuscular or other parenteral administration.

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.

Each vial of **RECOMBINATE** is labelled in accordance with the World Health Organisation International Standard for Factor VIII Concentrate with the Factor VIII activity expressed in IU per vial.
The expected *in vivo* peak increase in Factor VIII level expressed as IU/dL of plasma or % 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 findings and is supported by the data generated over time in 419 clinical pharmacokinetic studies with RECOMBINATE in 67 patients.

This data demonstrated a peak recovery point above the pre-infusion baseline of approximately 2.0IU/dL per IU/kg body weight.

Example (assuming patient's baseline Factor VIII level is at < 1%):
1) A dose of 1750IU RECOMBINATE administered to a 70kg patient, ie 25IU/kg body weight (1750IU/70), should be expected to cause a peak post-infusion Factor VIII increase of 25IU/kg x 2 (IU/dL)/(IU/kg) = 50IU/dL (50% of normal).
2) A peak level of 70% is required in a 40kg child. In this situation the dose would be 70IU/dL/2(IU/dL)/(IU/kg) x 40kg = 1400IU.

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

<table>
<thead>
<tr>
<th>Haemorrhage</th>
<th>Required peak post-infusion FVIII activity in the blood (as % of normal or IU/dL plasma)</th>
<th>Frequency of infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early haemarthrosis or muscle bleed or oral bleed</td>
<td>20 - 40</td>
<td>Infuse every 12 to 24 hours for one to three days until the bleeding episode is resolved (as indicated by pain) or healing is achieved.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleed, or haematoma</td>
<td>30 - 60</td>
<td>Repeat infusion every 12 to 24 hours for usually three days or more until pain and disability are resolved.</td>
</tr>
<tr>
<td>Life threatening bleeds such as head injury, throat bleed, severe abdominal pain</td>
<td>60 - 100</td>
<td>Repeat infusion every 8 to 24 hours until threat is resolved.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgery</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Operation</td>
<td></td>
</tr>
<tr>
<td>Minor surgery, including tooth extraction</td>
<td>60 - 80</td>
</tr>
<tr>
<td>Major surgery</td>
<td>80 - 100 (pre- and post-operative)</td>
</tr>
</tbody>
</table>
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 factor 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. Place vial on a flat surface.
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 DOSAGE AND ADMINISTRATION/Administration.)

**Administration: Use aseptic technique**

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

**Intravenous syringe injection**

RECOMBINATE should be inspected for particulate matter and discolouration after reconstitution and prior to administration. The solution should be colourless to faint yellow in appearance, and substantially free from foreign particles. If not, do not use the solution and notify Baxalta immediately.

Plastic syringes are recommended when administering RECOMBINATE, as proteins such as RECOMBINATE 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 that ensures the comfort of the patient, up to a maximum of 10mL per minute. 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. The Poison Information Centre at Phone Number: 131126 (in Australia) or 0800 764 766 [0800 POISON] in New Zealand, should be contacted for advice on the management of an overdosage.

PRESENTATION AND STORAGE CONDITIONS

Package

RECOMBINATE is available in three different strengths in single-dose vials, although not all strengths may be marketed. The strength is designated on the outer box and on the vial label using the following colour codes:

- Light blue bar: For low potencies of 250 IU (nominal) per vial
- Light pink bar: For medium potencies of 500 IU (nominal) per vial
- Light green bar: For high potencies of 1000 IU (nominal) 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°C - 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.

NAME AND ADDRESS OF THE SPONSOR

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DATE OF PREPARATION

22 September 2015

Based on Australian PI amended 18 September 2015, and CCSI 203 2015 0430.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.

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