

The following information is intended for medical or healthcare professionals only:

1. Name of the medicinal product

Recombinate 1000 IU powder and solvent for solution for injection

2. Qualitative and quantitative composition

Octocog alfa 100 IU per ml of reconstituted solution

After reconstitution: One vial of 10 ml contains 1000 IU octocog alfa

Recombinate 500 IU, is presented as a lyophilised powder for solution for injection, containing Recombinate 1000 IU, is presented as a lyophilised powder for solution for injection, containing nominally 1000 IU octocog alfa, recombinant, coagulation factor VIII per vial.

The product contains approximately 100 IU/ml octocog alfa, recombinant coagulation factor VIII when reconstituted with 10 ml of sterile water for injections.

The potency is determined using the European Pharmacopoeia chromogenic assay against the FDA Mega Standard calibrated to the WHO Standard. The specific activity of Recombinate is approximately 4000 - 8000 IU/mg protein.

Recombinate contains recombinant coagulation factor VIII (INN: octocog alfa). Octocog alfa (recombinant coagulation factor VIII) is a purified protein consisting of 2332 amino acids. It has an amino acid sequence that is comparable to factor VIII, and post-translational modifications that are similar to the plasma derived molecule. Recombinant coagulation factor VIII is a glycoprotein that is expressed by genetically engineered mammalian cells derived from a Chinese Hamster Ovary cell line.

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Powder and solvent for solution for injection.

White to off-white friable powder. The solvent (sterilised water for injections) is a clear and colorless liquid.

4. Clinical particulars

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with Hemophilia A (congenital Factor VIII deficiency).

This product does not contain von Willebrand factor and is therefore not indicated in von Willebrand's disease.

4.2 Posology and method of administration

4.2.1 Posology

The dosage and duration of the substitution therapy depends on the severity of the disorder of the hemostatic function, on the location and extent of bleeding episodes and on the clinical condition of the patient. The treatment should be carried out in collaboration with a physician with experience in bleeding disorders and a laboratory with the capacity to measure plasma AHF concentration.

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an International Standard of factor VIII in plasma). One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma. The expected in vivo peak increase in Recombinate 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.

The method calculation is illustrated in the following examples.

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

$$\text{Example for a 70 kg adult: } \frac{1750 \text{ IU} \times 2\% / \text{IU} / \text{kg}}{70 \text{ kg}} \approx 50\%$$

or

$$\text{Dosage required (IU): } \frac{\text{Body weight (kg)} \times \text{desired \% Factor VIII increase}}{2\% / \text{IU} / \text{kg}}$$

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

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 calculation 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. 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 (Bethesda Units) 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.

Recombinate is appropriate for the use in children of all ages, including the newborn (Safety and efficacy studies have been performed in both previously treated and previously untreated children; see section 5.1).

The following dosage schedule provided in Table I may be used as a guide for adults and children. The amount to be administered and the frequency of application should always be oriented to the clinical effectiveness in the individual case.

Recombinate may also be administered for prophylaxis (short or long term) of bleeding, as determined by the physician on an individual basis.

Table I: Dosage Schedule Hemorrhage

Degree of hemorrhage	Required peak post-infusion AHF activity in the blood (as % of normal or IU/dL plasma)	Frequency of infusion
Early hemarthrosis 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 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 intracranial bleed, throat bleed, severe abdominal bleed	60-100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery Type of operation Minor surgery, including tooth extraction	30-60	A single infusion plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases. Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80-100 (pre and post-operative)	Repeat infusion every 8 to 24 hours depending on state of healing.

This represents peak AHF activity for patients with the expected mean half-life for Factor VIII. If considered necessary, peak activity should be measured within one-half hour after administration. For patients with relatively short half-lives for Factor VIII it may be necessary to increase the dosage and/or frequency of administration.

Each vial of Recombinate is labelled with the Antihemophilic Factor (Recombinant), Recombinate activity expressed in IU per vial.

This potency assignment is referenced to the World Health Organization International Standard for Factor VIII Concentrate. Experiments have shown that, to achieve accurate activity levels, such a potency assay should be conducted using plastic test tubes and pipettes as well as substrate containing normal levels of von Willebrand Factor.

For long term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary. Patients should be monitored for the development of factor VIII inhibitors. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor VIII inhibitor is present. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia.

See also 4.4

4.2.2 Method of administration

The preparation is to be administered intravenously after reconstitution with the provided solvent (see section 6.6). It is recommended that administration commence within three hours after reconstitution. The reconstituted material should not be refrigerated. The preparation can be administered at a rate of up to 10 ml per minute. The pulse rate should be determined before and during administration of Recombinate. Should a significant increase occur, reducing the rate of administration or temporarily interrupting the injection usually allows the symptoms to disappear promptly. (See sections 4.4 and 4.8)

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. Known allergic reaction to bovine, mouse or hamster protein.

4.4 Special warnings and precautions for use

Severe allergic reactions to Recombinate have been reported. Patients with known hypersensitivity to mouse bovine or hamster proteins should be treated with caution. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If allergic or anaphylactic reactions occur, the injection/infusion should be stopped immediately. Facilities for the appropriate treatment of shock should be available.

If plasma AHF levels fail to reach expected levels or if bleeding is not controlled after adequate dosage, appropriate laboratory test to detect the presence of inhibitor should be performed.

The formation of neutralising antibodies (inhibitors) to Factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against Factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified Bethesda assay. 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. Rarely, inhibitors may develop after the first 100 exposure days. Cases of recurrence of inhibitors (low titre) have been observed after switching from one recombinant factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development.

Patients treated with recombinant coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. See also section 4.8.

In the interest of patients, it is recommended that, whenever possible, every time that Recombinate is administered to them, the name and batch number of the product should be registered.

This medicinal product contains 1.5 mmol sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interactions with other medicinal products and other forms of interaction

No interactions with other medicinal products have been observed.

4.6 Pregnancy and lactation

Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breastfeeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

As with the administration of any protein, adverse reactions may be encountered with the use of recombinant Antihemophilic Factor (rAHF) preparations. Adverse reactions occurring after infusion of rAHF have been reported in clinical studies to include: nausea, flushing, mild fatigue, rash, hematoma, diaphoresis, chills, shaking, fever, leg pain, cold hands and feet, sore throat, ear infection and failed hearing test, epistaxis and pallor. Sporadically, adverse events resembling allergic-type hypersensitivity have been reported in patients receiving commercial Recombinate. Allergic type symptoms may include hives, urticaria, rash, dyspnea, cough, chest tightness, wheezing, hypotension and anaphylaxis.

Patients should be informed of the early signs of hypersensitivity reactions and therefore should be advised to discontinue use of the product and contact their physician if these symptoms occur.

Caution is advised in patients with known allergic reactions to constituents of the preparation (See sections 4.3 and 4.4).

The formation of neutralizing antibodies, inhibitors, to Factor VIII is a known complication in the management of individuals with Hemophilia A. These inhibitors are invariably IgG immunoglobulins directed against the Factor VIII procoagulant activity, which are expressed as Bethesda Units (B.U.) per ml of plasma.

The risk of developing inhibitors is correlated to the exposure to Antihemophilic Factor VIII, this risk being highest within the first 20 exposure days. The reported incidence of inhibitory antibodies in patients with severe hemophilia A who are at high risk for inhibitor development (i.e., previously untreated patients) is estimated in studies to be 31% for Recombinate, which is within the reported range for plasma derived AHF. Patients treated with Recombinate should be carefully monitored for the development of inhibitory antibodies by appropriate clinical observations and laboratory tests.

The following table provides the frequency of patients with adverse drug reactions in clinical trials. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequency has been evaluated using the following criteria: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1 000, <1/100), rare (>1/10 000, <1/1 000), and very rare (<1/10 000).

MedDRA System Organ Class	Frequency of Clinical Adverse Drug Reactions (ADRs) for RECOMBinate	
	MedDRA Preferred Term	Frequency
Gastrointestinal disorders General disorders and administration site conditions	Nausea	uncommon
	Chills	common
	Fatigue	uncommon
	Pyrexia	uncommon
Infections and infestations Investigations	Ear infection	uncommon
	Acoustic stimulation tests abnormal	uncommon
Musculoskeletal and connective tissue disorders Nervous system disorders	Pain in extremity	uncommon
	Dizziness	uncommon
Respiratory, thoracic and mediastinal disorders Skin and subcutaneous tissue disorders	Tremor	uncommon
	Pharyngolaryngeal pain	uncommon
	Hyperhidrosis	uncommon
Vascular disorders	Pruritus	uncommon
	Rash	uncommon
	Rash maculo-papular	uncommon
	Epistaxis	uncommon
	Flushing	uncommon
	Haematoma	uncommon
	Hypotension	uncommon
Pallor	uncommon	
	Peripheral coldness	uncommon

¹ Number of evaluable subjects experiencing the event/total number of evaluable subjects [% relative to 210, the total number of unique subjects who received at least one infusion of Recombinate]

² Number of times the event was experienced/total number of infusions [% relative to 25,915, the total number of infusions of Recombinate]

In the spontaneous, post-marketing database, there have been reports of cyanosis, tachycardia, vomiting, abdominal discomfort, anaphylactic shock, hypersensitivity, syncope, headache, skin exfoliation and inhibitor to FVIII.

4.9 Overdose

No symptoms of overdose are known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: antihemorrhagics: blood coagulation factor VIII. ATC code: B02BD02.

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions.

When infused into a haemophilic patient, factor VIII binds to von Willebrand factor in the patient's circulation.

Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Recombinate has been studied in 71 previously untreated children (PUP's). Median age of the cohort at the time of first Recombinate infusion was 10 months (range: 2 days to 50 months). The product was well tolerated and not associated with significant short-term adverse effects. Its clinical efficacy was comparable to other full-length FVIII molecules in both the treatment of acute haemorrhage and

for surgical prophylaxis (10 subjects had undergone surgical interventions). Long-term follow-up of the cohort revealed an incidence of product-related adverse events of 0.86/1000 infusions, none serious or life-threatening.

5.2 Pharmacokinetic properties

Pharmacokinetic studies on 69 previously treated patients revealed the circulating mean half-life for Recombinate to be 14.6 ± 4.9 hours (n=67), which was not statistically significantly different from plasma-derived Antihemophilic Factor (Human), Hemofil®M, (pdAHF). The mean half-life of Hemofil®M was 14.7 ± 5.1 hours (n=61). The actual baseline recovery observed with Recombinate after infusion of a 50 IU/kg dose was 123.9 ± 47.7 IU/dl (n=23), which is significantly higher than the actual Hemofil®M baseline recovery of 101.7 ± 31.6 IU/dl (n=61). However, the calculated ratio of actual to expected recovery (i.e., 2% increment in Factor VIII activity 1 IU rAHF/kg body weight) with Recombinate ($121.2 \pm 48.9\%$) is similar to that of Hemofil®M ($123.4 \pm 16.4\%$)

A total of 494 recovery studies were obtained from 68 previously untreated patients. Two hundred and twelve recovery studies were performed when the patients were being treated for bleeds with a mean \pm SD actual recovery of 70.0 ± 37.9 IU/dL (N=208), four recoveries omitted from analysis as outliers). The high variability is due to the wide range of actual dose given, 13.8 to 103.2 IU/kg (mean \pm SD of 36.0 ± 16.2 and median of 30.2 IU/kg). To account for the variable dosing levels, the actual/predicted recovery ratios were calculated, resulting in a mean of 1.0 ± 0.3 .

A total of 68 recovery studies were performed when the patients were receiving a follow-up infusion for continued treatment of a pre-existing bleed. The actual FVIII recovery level was corrected for the pre-infusion FVIII level. The mean \pm SD actual recovery was 88.6 ± 38.2 IU/dL (N= 66) with two recoveries omitted from the analysis as outliers). Again, the wide range of actual doses given, 18.5 to 85.7 IU/kg (mean \pm SD of 38.6 ± 15.9 and median of 32.1 IU/kg) results in substantial variation in the recovery levels observed. The mean \pm SD actual/predicted recovery ratio was 1.0 ± 0.3 with a median of 1.0.

A total of 214 recovery studies were performed when patients were in stable state resulting in a mean actual recovery of 71.6 ± 29.7 IU/dL (N= 209) with five recoveries omitted from the analysis as outliers). The doses given ranged from 10.4 to 68.1 IU/kg (mean \pm SD of 38.0 ± 12.7 and median of 36.1 IU/kg). The mean \pm SD actual/predicted recovery ratio was 1.0 ± 0.3 .

5.3 Preclinical safety data

Recombinant acts like the endogenous factor VIII. Doses several times the recommended human dosage per kilogram body weight show no toxic effects on laboratory animals. Recombinate was tested for mutagenicity at doses considerably exceeding plasma concentrations of AHF in vitro and at doses up to ten times the expected maximum clinical dose in vivo, and did not cause reverse mutations, chromosomal aberrations, or an increase in micronuclei in bone marrow polychromatic erythrocytes. Since clinical experience provides no evidence for tumorigenic and mutagenic effects, long term studies in animals to evaluate carcinogenic potential are not considered imperative.

6. Pharmaceutical particulars

6.1 List of excipients

Powder:
Human Albumin
Sodium Chloride
Histidine
Macrogol 3350
Calcium Chloride Dihydrate

Solvent:

Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products or solvents.

Only the provided infusion sets should be used because treatment failure can occur as a consequence of human coagulation factor VIII adsorption to the internal surfaces of some infusion equipment.

6.3 Shelf-life

Two years. After reconstitution, Recombinate should not be refrigerated and should be administered within three hours.

6.4 Special precautions for storage

Store in a refrigerator ($2^{\circ}\text{C} - 8^{\circ}\text{C}$).

Do not freeze.

Store in the outer carton in order to protect from light.

Within its shelf-life, the product may be stored at $15^{\circ}\text{C} - 25^{\circ}\text{C}$ prior to use for up to six months.

Do not return to refrigeration following storage at $15^{\circ}\text{C} - 25^{\circ}\text{C}$.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

A single pack contains a p vial, a 10 ml solvent vial (both type I glass with rubber stoppers) and a device for reconstitution (BAXJECT II) + one sterile single-use plastic syringe + one sterile mini-infusions set + 2 alcohol swabs + 2 plasters.

Alternatively to BAXJECT II a needle device for reconstitution comprising one sterile double-ended needle (to transfer the solvent into the Recombinate vial), one sterile filter needle (to transfer the reconstituted solution into the syringe) can be provided.





Pack size of 1



6.6 Special precautions for disposal and other handling

The preparation is to be administered intravenously after reconstitution with the provided Sterilised Water for Injections. The disposable plastic syringe provided with the product should be used.

- Use within three hours after reconstitution.
- Do not refrigerate preparation after reconstitution.
- Any unused product or waste material should be disposed of in accordance with local requirements.
- The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.

Do not use if the product, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.

Reconstitution: Use Aseptic Technique	
Reconstitution with BAXJECT II	Reconstitution with needles
1. Bring Recombinate (powder) and Sterilised Water for Injections (solvent) to $15-25^{\circ}\text{C}$.	1. Bring Recombinate (powder) and Sterilised Water for Injections (solvent) to $15-25^{\circ}\text{C}$.
2. Remove caps from powder and solvent vials.	2. Remove caps from powder and solvent vials
3. Cleanse stoppers with alcohol swabs. Place the vials on a flat surface.	3. Cleanse stoppers with alcohol swabs. Place the vials on a flat surface.
4. Open the package of BAXJECT II device by peeling away the paper lid without touching the inside (Fig. a). Do not remove the device from the package.	4. Remove protecting covering from one end of double-ended needle and insert exposed needle through stopper.
5. Turn the package over and insert the clear plastic spike through the solvent stopper. Grip the package at its edge and pull the package off BAXJECT II (Fig. b). Do not remove the blue cap from BAXJECT II device.	5. Remove protective covering from other end of double-ended needle. Invert solvent vial over the upright Recombinate vial, then rapidly insert free end of the needle through the Recombinate vial stopper at its center. The vacuum in the vial will draw in the solvent.
6. With BAXJECT II attached to the solvent vial, invert the system so that the solvent vial is on top of the device. Insert the white plastic spike through the Recombinate stopper. The vacuum will draw the solvent into the Recombinate vial (Fig. c).	6. Disconnect the two vials by removing needle from solvent vial stopper, then remove needle from Recombinate vial. Swirl gently until all material is dissolved. Be sure that Recombinate is completely dissolved, otherwise active material will be removed by the filter needle.
7. Swirl gently until all material is dissolved. Be sure that Recombinate is completely dissolved; otherwise active material will not pass through the device filter. The product dissolves rapidly (usually in less than 1 minute).	
Fig. a	Fig. b
	
	

Administration: Use Aseptic Technique	
It is recommended that administration commence within three hours after reconstitution. The reconstituted material should not be refrigerated. Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. A colourless to faintly yellow appearance is acceptable for Recombinate.	It is recommended that administration commence within three hours after reconstitution. The reconstituted material should not be refrigerated. Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. A colourless to faintly yellow appearance is acceptable for Recombinate.
1. Remove the blue cap from BAXJECT II. DO NOT DRAW AIR INTO THE SYRINGE. Connect the syringe to BAXJECT II (Fig. d).	1. Attach filter needle to the disposable syringe and draw back plunger to admit air into syringe.
2. Invert the system (with concentrate vial on top). Draw the concentrate into the syringe by pulling the plunger back slowly (Fig. e).	2. Insert filter needle into reconstituted Recombinate
3. Insert filter needle into reconstituted Recombinate	3. Inject air into vial and then withdraw the reconstituted material into the syringe.
4. Attach the administration set to the syringe. Inject intravenously. The preparation can be administered at a rate of up to 10 ml per minute. The pulse rate should be determined before and during administration of Recombinate. Should a significant increase occur, reducing the rate of administration or temporarily interrupting the injection usually allows the symptoms to disappear promptly. (See sections 4.4 and 4.8).	4. Remove and discard filter needle. Attach administration set to the syringe. Inject intravenously. The preparation can be administered at a rate of up to 10 ml per minute. The pulse rate should be determined before and during administration of Recombinate. Should a significant increase occur, reducing the rate of administration or temporarily interrupting the injection usually allows the symptoms to disappear promptly. (See sections 4.4 and 4.8).
Fig. d	Fig. e
	
	5. A separate unused filter needle must be used to withdraw each vial of reconstituted Recombinate.