Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Recombinate 500 IU, powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Octocog alfa 50 IU per ml of reconstituted solution
After reconstitution: One vial of 10 ml contains 500 IU octocog alfa
Recombinate 500 IU, contains nominally 500 IU octocog alfa, recombinant, coagulation factor VIII per vial.
The product contains approximately 50 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.
Excipients with known effect: sodium
For the 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 (sterilized water for injections) is a clear and colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment and prophylaxis of bleeding in patients with Haemophilia A (congenital Factor VIII deficiency).
This product does not contain von Willebrand factor and is therefore not indicated in von Willebrand's disease.
Recombinate is indicated for all age groups from neonates to adults.

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 haemostatic 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 of calculation is illustrated in the following examples.

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

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

70 kg

Or

Dosage required (IU): Body weight (kg) x desired % Factor VIII increase

2% / IU / kg

Example for a 40 kg child: 40 kg x 70% = 1400 IU

2% / IU / kg

The careful control of the substitution therapy is especially important in cases of major surgery or life threatening haemorrhages. 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 an 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 titres above 10 Bethesda Units per ml may make haemostasis control with AHF either impossible or impractical because of the very large dose required.
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
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 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 of Factor VIII. If considered necessary, peak activity should be measured within one-half hour after administration. For patients with relatively short half-lives of Factor VIII it may be necessary to increase the dosage and/or frequency of administration.
Each vial of Recombinate is labelled with the Antihaemophilic Factor (Recombinant), Recombinate activity expressed in IU per vial.

This potency assignment is referenced to the World Health Organization International Standard for Factor VIII:C 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.
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.
Paediatric population:
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). For on-demand treatment, dosing in paediatric patients does not differ from adult patients. For long term prophylaxis against bleeding in patients with severe haemophilia A, in some cases shorter dosage intervals or higher doses may be necessary than the usual doses of 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days.

4.2.2 Method of administration

The preparation is to be administered intravenously after reconstitution with the provided solvent (see section 6.6). The reconstituted material should not be refrigerated. It is advised to administer Recombinate at room temperature not more than 3 hours after reconstitution. The rate of administration should be such that it ensures the comfort of the patient, up to a maximum of 10 ml/min. 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)
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. 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.

Inhibitors
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 the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently low titre posing less of a risk of insufficient clinical response than high titre inhibitors. In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. 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 haemophilia and factor VIII inhibitors.

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 vial. To be taken into consideration by patients on a controlled sodium diet.

Paediatric population
The warnings and precautions for use in paediatric patients do not differ from those for adult patients.

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed.

4.6 Fertility, 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 breast-feeding 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

Tabulated summary of adverse reactions
The following table lists the adverse reactions observed from spontaneous reporting and 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), very rare (<1/10 000) and not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Frequency**	**MedDRA Preferred Term**
Infections and infestations	uncommon	Ear infection
Blood and lymphatic system disorders	Uncommon (PTPs)[1] Very Common (PUPs)[1]	Factor VIII inhibition[1]
Immune system disorders	not known	Anaphylactic reaction Hypersensitivity[2]
Nervous system disorders	uncommon	Dizziness Tremor
	not known	Loss of consciousness Syncope Headache Paresthesia
Cardiac disorders	not known	Cyanosis Tachycardia
Vascular disorders	uncommon	Epistaxis Flushing Haematoma Hypotension Pallor Peripheral coldness
Respiratory, thoracic and mediastinal disorders	uncommon	Pharyngolaryngeal pain
	not known	Dyspnea Cough Wheezing
Gastrointestinal disorders	uncommon	Nausea
	not known	Vomiting Abdominal pain
Skin and subcutaneous tissue disorders	uncommon	Hyperhydrosis Pruritus Rash Rash maculo-papular
	not known	Angioedema Urticaria Skin exfoliation Erythema

Musculoskeletal and connective tissue disorders	uncommon	Pain in extremity
General disorders and administration site conditions	common	Chills
	uncommon	Fatigue Pyrexia
	not known	Malaise Injection site reactions Chest pain Chest discomfort
Investigations	uncommon	Acoustic stimulation tests abnormal

[1] Frequency is based on studies with all FVIII products which induced patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients.
[2] Early signs of hypersensitivity reactions are e.g. urticaria, dyspnea, cough, chest discomfort, wheezing,anaphylaxis, rash, hypotension, pruritus, chills, flushing, pyrexia, cyanosis, tachycardia, vomiting, syncope, headache. Caution is advised in patients with known allergic reactions to constituents of the preparation (See sections 4.3 and4.4).

Description of selected adverse reactions
Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with Recombinate. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialized haemophilia centre be contacted.

Paediatric population
Other than the development of inhibitors in previously untreated paediatric patients (PUPs), no age-specific differences in ADRs were noted in the clinical studies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 6762517. Website: http://www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

No symptoms of overdose are known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: antihaemorrhagics: 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 haemophiliac 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 Antihaemophilic Factor (Human), HemofilM, (pdAHF). The mean half-life of HemofilM 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 HemofilM 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 ± 48.9%) is similar to that of HemofilM (123.4 ± 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 ± 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 ± 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 ± 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 ± SD of 38.6 ± 15.9 and median of 32.1 IU/kg) results in substantial variation in the recovery levels observed. The mean ± 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 ± SD of 38.0 ± 12.7 and median of 36.1 IU/kg). The mean ± SD actual/predicted recovery ratio was 1.0 ± 0.3.

5.3 Preclinical safety data

Recombinate 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
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

Solvent:
Water for Injections

6.2 Incompatibilities

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

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

3 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°C – 8°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°C - 25°C prior to use for up to six months.
Do not return to refrigeration following storage at 15°C - 25°C.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

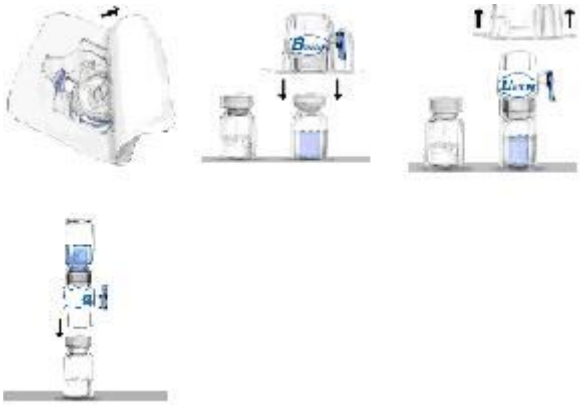
6.5 Nature and contents of container

A single pack contains a powder 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

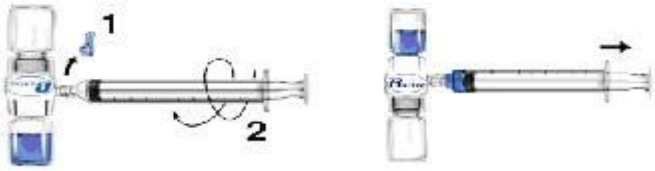
6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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.
- o Use within three hours after reconstitution.
- o Do not refrigerate preparation after reconstitution.

o Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
o 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.
o 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°C. 2. Remove caps from powder and solvent vials. 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. 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. 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). 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 Fig. c** 	1. Bring Recombinate (powder) and Sterilised Water for Injections (solvent) to 15-25°C. 2. Remove caps from powder and solvent vials. 3. Cleanse stoppers with alcohol swabs. Place the vials on a flat surface. 4. Remove protecting covering from one end of double-ended needle and insert exposed needle through stopper of solvent vial. 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. 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.

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. 1. Remove the blue cap from BAXJECT II. DO NOT DRAW AIR INTO THE SYRINGE. Connect the syringe to BAXJECT II (Fig. d). 2. Invert the system (with concentrate vial on top). Draw the concentrate into the syringe by pulling the plunger back slowly (Fig. e). 3. Disconnect the syringe. 4. Attach the administration set to the syringe. Inject intravenously. The preparation can be	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

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**  	administration, whenever solution and container permit. A colourless to faintly yellow appearance is acceptable for Recombinate. 1. Attach filter needle to the disposable syringe and draw back plunger to admit air into syringe. 2. Insert filter needle into reconstituted Recombinate. 3. Inject air into vial and then withdraw the reconstituted material into the syringe. 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). 5. A separate unused filter needle must be used to withdraw each vial of reconstituted Recombinate.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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