APPROVED PACKAGE INSERT

SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM
IMMUNATE 250 IU POWDER AND SOLVENT FOR SOLUTION FOR INJECTION
IMMUNATE 500 IU POWDER AND SOLVENT FOR SOLUTION FOR INJECTION
IMMUNATE 1000 IU POWDER AND SOLVENT FOR SOLUTION FOR INJECTION

COMPOSITION
IMMUNATE is presented as powder and solvent for solution for injection containing nominally 250 IU (500 IU / 1000 IU) human coagulation factor VIII per vial
The product contains approximately 50 IU/ml (250 IU pack size) or 100 IU/ml (500 IU and 1000 IU pack size) of human coagulation factor VIII and at least 25 U/ml (250 IU pack size) or 50 U/ml (500 IU and 1000 IU pack size) of von Willebrand factor when reconstituted with 5 ml (250 IU and 500 IU pack size) or 10 ml (1000 IU pack size) of Sterilised Water for Injection. All blood donors are volunteers

The other ingredients are:

Albumin (Human) 20 %	5,8 – 15 mg (250 IU pack size) 11,7 – 30 mg (500 IU pack size) 23,3 – 60 mg (1 000 IU pack size)
Glycine	25 mg
Lysine monohydrochloride	25 mg
Sodium chloride	10 mg
Trisodium citrate dihydrate	25 mg
Calcium chloride dihydrate	3,1 mg

The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of IMMUNATE is approximately 70 ± 30 IU/mg protein.

PHARMACOLOGICAL CLASSIFICATION
A 30.3: Blood fraction

PHARMACOLOGICAL ACTION
Pharmacodynamic properties
The factor VIII/von Willebrand factor complex consists of two molecules (FVIII and vWF) with different physiological functions.
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 to 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 and 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.
In addition to its role as a FVIII protecting protein, vWF mediates platelet adhesion to sites of vascular injury, plays a role in platelet aggregation and is indispensable for substitution therapy in patients with von Willebrand's disease.

Pharmacokinetic properties
After injection, the level of factor VIII activity reached in the plasma is between 80 % - 120 % of the predicted plasma factor VIII activity. In a pharmacokinetic study, the mean in vivo recovery of factor VIII after administration of IMMUNATE was determined to be approximately 100%.
Kinetics may follow one or two phases of plasma factor VIII activity decrease. When plasma factor VIII activity decreases a two-phase exponential decay, distribution between the intravascular and other compartments (body fluids) occurs with a half-life of elimination from the plasma of 3 to 6 hours in the initial phase; approximately two thirds to three quarters of the factor VIII remain in the circulation. In the subsequent slower phase (which probably reflects the consumption of factor VIII), the half-life varies between 8-20 hours, with an average of 12 hours. This appears to correspond to the true biological half-life. In the above mentioned study with IMMUNATE, the half-life of factor VIII was determined by model dependent as well as model independent methods.

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Mean values obtained were in both cases approximately 11 hours. Model-independent analysis resulted in mean residence time of 16 hours, mean clearance was approximately 4 ml/hour/kg, and the apparent volume of distribution showed a mean of 58 ml/kg after IMMUNATE infusion.

In a complementary study of repeated recovery and half-life the median changes in in-vivo recovery and half-life of IMMUNATE in the same patients at an interval of three to six months were +7,2 % for in-vivo recovery, and -5,3 % for non-compartmental half-life. In addition, the model-dependent analysis was used to determine that elimination was biphasic rather than monophasic in most patients.

Preclinical safety data
Human blood coagulation factor VIII (contained in **IMMUNATE**) is a normal constituent of the human plasma and acts like the endogenous factor VIII.
Single dose toxicity testing is of no relevance since higher doses result in overloading.
Even doses of several times the recommended human dosage per kilogram body weight show no toxic effects on laboratory animals.
Repeated dose toxicity testing in animals is impracticable due to interference with developing antibodies to heterologous protein.
Since clinical experience provides no evidence of tumorigenic or mutagenic effects of human blood coagulation factor VIII, experimental studies, particularly in heterologous species, are not considered imperative.

INDICATIONS
Therapeutic indications
- Treatment and prophylaxis of bleeding in patients with congenital factor VIII deficiency or acquired factor VIII deficiency (haemophilia A, haemophilia A with factor VIII inhibitor, acquired factor VIII deficiency due to spontaneous development of factor VIII inhibitor).
- Treatment of bleeding in patients with Von Willebrand's disease with factor VIII deficiency.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients.

WARNINGS
As with any intravenous protein product, allergic type hypersensitivity reactions are possible. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, they should be advised to discontinue use of the product immediately and contact their physician.
In the case of shock, the current medical standards tor shock-treatment should be observed.

As the quantity of sodium in the maximum daily dose may exceed 200 mg, it may be harmful to people on a low sodium diet.

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 lgG 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 exposure to anti-haemophilic factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Patient treated with human coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory testing.

The product should be used with caution in children less than 6 years of age, who have limited exposure to factor VIII products, as there is limited clinical data available for this patient group.

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of unknown nature. The risk of transmission of infective agents is however reduced by:
- selection of donors by a medical interview and screening of individual donations and plasma pools for HBsAg and antibodies to HIV and HCV.

- testing of plasma pools for genomic material of HIV-1, HIV-2, HAV, HBV, HCV, and parvovirus B19.
- viral inactivation/removal procedures included in the production process that have been validated using target and/or model viruses. These procedures are considered effective for HIV-1. HIV-2, HAV, HBV and HCV.

The viral inactivation/removal procedures may be of limited value against non-enveloped viruses such as parvovirus B19.
Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased red cell turnover (e.g. in haemolytic anaemia).
Appropriate vaccination (hepatitis A and B) for patients receiving plasma derived Factor VIII concentrates is recommended.
In the interest of patients, it is recommended that, whenever possible, the name and batch number of the product is recorded every time IMMUNATE is administered to them.

INTERACTIONS
No interactions of human coagulation factor VIII products with other medicinal products are known.

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.

DOSAGE AND DIRECTIONS FOR USE
Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia.

Posology
The dosage and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and on the patient's clinical condition.
The number of units of factor VIII administered is expressed in International Units (IU), which is 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 for Factor VIII concentrates).
One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in 1 ml of normal human plasma.

Dosage in Haemophilia A
The calculation of the required dosage of factor VIII as specified below is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by 1,5% to 2% of normal activity.
The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor VIII rise (%) x 0,5

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

Haemorrhages and Surgery
In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dl) in the corresponding period.

The following table can be used to guide dosing in bleeding episodes and surgery:

Degree of haemorrhage / Type of surgical procedure	F VIII level required (% of normal) (IU/dl)	Frequency of Doses (hours) / Duration of Therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20 - 40	Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma	30 - 60	Repeat infusion every 12 – 24 hours for 3 – 4 days or more until pain and acute disability are

Life threatening haemorrhages	60 - 100	resolved Repeat infusion every 8 to 24 hours until threat is resolved
Surgery *Minor* Including tooth extraction *Major*	30 - 60 80 – 100 (pre- and postoperative)	Every 24 hours, at least 1 day, until healing is achieved. Repeat infusion every 8 – 24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30 % to 60 % (IU/dl)

The amount and frequency of administration should be adapted to the clinical response in the individual case. Under certain circumstances (e.g. presence of a low titre inhibitor) doses larger than those calculated using the formula may be necessary.

During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable. Individual patients may vary in their response to factor VIII, achieving different levels of *in-vivo* recovery and demonstrating different half-lives.

Long term prophylaxis
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.

Haemophiliacs with inhibitor to factor VIII
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.

Von Willebrand's desease with factor VIII deficiency
IMMUNATE is indicated for factor VIII replacement therapy in patients with von Willebrand's disease in whom factor VIII activity is reduced. Replacement therapy with IMMUNATE to control haemorrhages and to prevent bleeding episodes associated with surgical interventions follows the guidelines given for haemophilia A.

Method of administration
IMMUNATE should be administered slowly via the intravenous route. The rate of administration should be determined, at a rate that ensures the comfort of the patient up to a maximum of 2 ml per minute.

IMMUNATE is to be reconstituted only immediately before administration. The solution should then be used immediately (preparation does not contain preservatives). Solutions that are turbid or have deposits must not be used. It is advisable to rinse a common venous access with isotonic saline prior to and after infusion of IMMUNATE.

Reconstitution of dried substance: Use Aseptic Technique as described below
1. Warm the unopened vial containing the solvent (Sterilised Water for Injections) to room temperature (maximum 37 °C).
2. Remove protective caps from the concentrate vial and solvent vial (fig. A) and cleanse the rubber stoppers of both.
3. Place and press the undulated rim of the transfer set onto the solvent vial (fig. B).
4. Remove protective covering from the other end of the transfer set taking care not to touch the exposed end.

5. Invert the transfer set with the attached solvent vial over the concentrate vial and insert the free needle through the rubber stopper of the concentrate vial (fig. C). The solvent will be drawn into the concentrate vial by vacuum.
6. After approximately one minute, disconnect the two vials by removing the transfer set with the attached solvent vial from the concentrate vial (fig. D). Since the preparation dissolves easily, only gently - if at all - agitate the concentrate vial. DO NOT SHAKE THE CONTENTS OF THE VIAL. DO NOT INVERT THE CONCENTRATE VIAL UNTIL READY TO WITHDRAW CONTENTS.
7. After reconstitution, the prepared solution should be inspected visually for particulate matter and discoloration prior to administration. However, even when the reconstitution procedure is strictly followed, a few small particles may occasionally be visible. The enclosed filter set will remove particles and the labeled potency will not be reduced.

Administration: Use Aseptic Technique as described below

1. To prevent stopper-derived rubber particles from being administered with the medicinal product (risk of microembolism), use the enclosed filter set. To withdraw the dissolved preparation, fit the filter set onto the enclosed disposable syringe and insert it through the rubber stopper (fig. E).
2. Disconnect the syringe for a moment from the filter set. Air will enter into the concentrate vial and any foam will collapse. Then draw the solution into the syringe through the filter set (fig. F).
3. Disconnect the syringe from the filter set and slowly inject the solution intravenously (maximum rate of injection: 2 ml per minute) with the enclosed winged infusion set (or the enclosed disposable needle).

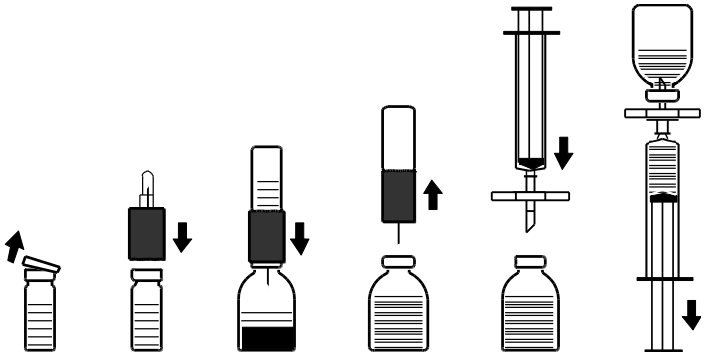

fig. A fig. B fig. C fig. D fig. E fig. F

All unused solution, empty vials and used needles and syringes must be discarded appropriately.

SIDE EFFECTS

The undesirable effects reported in the listings hereafter are based on reports from clinical trials and on post-marketing experience for IMMUNATE. Their frequency has been evaluated by 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)

Clinical trials

The incidence rate is uncommon (>1/1,000, <1/100), for all the Adverse Events reported below.

Immune system disorder

Allergic reaction

Post Marketing Experience

The incidence rate is <1/10,000, i.e. very rare, for all the Adverse Events reported below.

Blood and lymphatic system disorders

- Antibodies (Inhibitors) to Factor VIII
- Haemolysis in blood group A, B or /AB patients

Immune system disorders

- Angioedema
- Urticaria (Generalised)
- Hives

Nervous system disorders

- Headache

- Restlessness
- Tingling

Cardiac disorders
- Tachycardia

Vascular disorders
- Flushing
- Hypotension

Respiratory, thoracic and mediastinal disorder
- Wheezing

Gastrointestinal disorders
- Nausea
- Vomiting

General disorders and administration site conditions
- Burning and slinging at the infusion site
- Chills
- Lethargy
- Tightness of the chest
- Fever
- Therapeutic response decreased

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed very rare, and may in very rare cases progress to severe anaphylaxis (including shock).
On very rare occasions, fever has been observed.

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted
Following administration of large doses (e.g. when more than 100% of plasma Factor VIII levels are intended), hemolysis may occur in blood group A. B or AB patients, due to the presence of isoagglutinins in the product.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
No symptoms of overdose with human coagulation factor VIII have been reported.

IDENTIFICATION
A lyophilised, white or pale yellow powder or friable solid in vials of surface-treated soda lime glass hydrolytic type II.
The solvent is in vials of neutral glass hydrolytic type I. The product vials are closed with chlorobutyl rubber stoppers, the solvent vials with bromobutyl rubber stoppers.
The reconstituted product is a colourless to slightly yellowish and clear to slightly opalescent solution.

PRESENTATION
IMMUNATE is available in sizes of 250 IU, 500 IU and 1000 IU, to be dissolved in 5 ml (250 IU and 500 IU pack size) or 10 ml (1000 IU pack size) of Sterilised Water for Injections. Both powder and solvent come in single dose glass vials (powder: surface-treated soda lime silica glass, hydrolytic type II; solvent: neutral glass, hydrolytic type I) closed by either halogenobutyl rubber or fluoro-resin laminated butyl rubber stoppers. Each pack also includes a kit for reconstitution and injection comprising a transfer/filter set, a disposable syringe, a disposable needle, and a winged infusion set.
Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS
Store at 2 °C to 8 °C. Do not freeze. Store in the original package to protect from light.
During the shelf life the product may be kept at room temperature (up to 25 °C) for a single period not exceeding 6 months. Record the period of storage at room temperature below the expiration date

indicated on the product package. At the end of this period the product should not be put back in the refrigerator but should be used or discarded.
IMMUNATE should be administered at room temperature. Stability studies support the stability of the reconstituted product for 3 hours. Nevertheless, from a microbiological viewpoint, the product should be used immediately after reconstitution.

REGISTRATION NUMBER
IMMUNATE 250 IU: A40/30.3/0215
IMMUNATE 500 IU: A40/30.3/0216
IMMUNATE 1000 IU: A40/30.3/0217

NAME AND BUSINESS ADDRESS OF HOLDER OF THE CERTIFICATE OF REGISTRATION
Takeda (Pty) Ltd
Building A
Monte Circle, Monte Casino Boulevard
Fourways 2191 Gauteng
South Africa

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