Professional Information

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

IMMUNATE 250 IU POWDER AND SOLVENT FOR SOLUTION FOR INJECTION

IMMUNATE 500 IU POWDER AND SOLVENT FOR SOLUTION FOR INJECTION

IMMUNATE 1 000 IU POWDER AND SOLVENT FOR SOLUTION FOR INJECTION

2 QUALITATIVE AND QUANTITATIVE 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

Sugar Free

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

Excipient(s) with known effect:

Sodium 9,8 mg per vial (250 IU and 500 IU pack size) and 19,6 mg per vial (1 000 IU pack size).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White or pale yellow powder or friable solid.

4 CLINICAL PARTICULARS

4.1 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.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia.

Treatment monitoring

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.

Dose based on bodyweight may require adjustment in underweight or overweight patients.

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 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 resolved
Life threatening haemorrhages	60 - 100	Repeat infusion every 8 to 24 hours until threat is resolved
Surgery		
Minor Including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved.

Degree of haemorrhage / Type of surgical procedure	F VIII level required (% of normal) (IU/dl)	Frequency of Doses (hours) / Duration of Therapy (days)
Major	80 – 100 (pre- and postoperative)	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.

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 disease 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.

Since IMMUNATE contains a relatively high amount of factor VIII in relation to vWF, the treating physician should be aware that continued treatment may cause an excessive rise in factor VIII:C, which can lead to an increased risk of thrombosis.

Paediatric population

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 are limited data available for this patient group.

Dosing in haemophilia A in children and adolescents aged < 18 years old is based on body weight and is therefore generally based on the same guidelines as for adults. The amount and frequency of administration should always be oriented to the clinical effectiveness in the individual case (see section 4.4). In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

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.

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.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded

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 for shock-treatment should be observed.

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 severity of the disease as well as the exposure to anti-haemophilic factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon. Patient treated with human coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory testing.

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.

Cardiovascular events
In patients with existing cardiovascular risk factors, substitution therapy with FVIII may increase the cardiovascular risk.

Inhibitors (Patients with von Willebrand's disease)

Patients with von Willebrand disease, especially type 3 patients, may develop neutralizing antibodies (inhibitors) to von Willebrand factor. If the expected VWF:RCo activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an appropriate assay should be performed to determine if a von Willebrand factor inhibitor is present. In patients with high levels of inhibitor, von Willebrand factor therapy may not be effective and other therapeutic options should be considered.

Thrombotic events

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors. Therefore, patients must be monitored for early signs of thrombosis. Prophylaxis against venous thromboembolism should be instituted, according to the current recommendations. Since Immunate contains a relatively high amount of factor VIII in relation to VWF, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C. In patients receiving Immunate, plasma levels of FVIII:C should be monitored to avoid sustained excessive FVIII:C plasma levels, which may increase the risk of thrombotic events.

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.

Sodium content

250 IU and 500 IU pack size

This medicinal product contains 9,8 mg sodium per vial, equivalent to 0,5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

1 000 IU pack size

This medicinal product contains 19,6 mg sodium per vial, equivalent to approximately 1 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

There is no information on the effects of Immunate on the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects based on reports from clinical trials and on post-marketing experience for Immunate:

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention:

very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

MedDRA Standard System Organ Class	**Adverse Reaction**	**Frequency**
Immune system disorders	Hypersensitivity	Uncommon[1]
Blood and lymphatic system disorders	Factor VIII inhibition	Uncommon (PTPs)[2] Very common (PUPs)[2]
	Coagulopathy	Unknown
Psychiatric disorders	Restlessness	Unknown
Nervous system disorders	Paraesthesia	Unknown
	Dizziness	Unknown
	Headache	Unknown
Eye disorders	Conjunctivitis	Unknown
Cardiac disorders	Tachycardia	Unknown
	Palpitations	Unknown
Vascular disorders	Hypotension	Unknown
	Flushing	Unknown
	Pallor	Unknown
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Unknown
	Cough	Unknown
Gastrointestinal disorders	Vomiting	Unknown

MedDRA Standard System Organ Class	**Adverse Reaction**	**Frequency**
	Nausea	Unknown
Skin and subcutaneous tissue disorders	Urticaria	Unknown
	Rash (including erythematous and papular rash)	Unknown
	Pruritus	Unknown
	Erythema	Unknown
	Hyperhidrosis	Unknown
	Neurodermatitis	Unknown
Musculoskeletal and connective tissue disorders	Myalgia	Unknown
General disorders and administration site conditions	Chest pain	Unknown
	Chest discomfort	Unknown
	Oedema (including peripheral, eyelid and face oedema)	Unknown
	Pyrexia	Unknown
	Chills	Unknown
	Injection site reactions (including burning)	Unknown
	Pain	Unknown

[1] One hypersensitivity reaction in 329 infusions in one clinical trial in 5 patients.

[2] Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients.

Description of selected adverse reactions

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, rash, headache, hives, pruritus, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, dyspnoea, tingling, vomiting, wheezing) have been

observed rarely and may in some cases progress to severe anaphylaxis (including shock). Patients should be advised to contact their physician if these symptoms occur (see section 4.4).

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with Immunate. 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Additionally, suspected adverse reactions can be reported to AE.SouthafricaSSA@takeda.com or on the 24 hours contact number: 082 525 3040

4.9 Overdose

No symptoms of overdose with human coagulation factor VIII have been reported.

Thromboembolic events may occur. See section 4.4.

Haemolysis may occur in patients with blood group A, B, or AB. See section 4.4.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Class: A 30,3 Blood Fractions

Pharmacotherapeutic Group: anti-haemorrhagics: von Willebrand factor and coagulation factor VIII in combination. ATC code: B02BD06.

Mechanism of action

The factor VIII/von Willebrand factor complex consists of two molecules (FVIII and vWF) 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 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.

5.2 Pharmacokinetic properties

All pharmacokinetic parameters for Immunate were measured in subjects with severe Haemophilia A (factor VIII level ≤ 1 %). The analysis of plasma samples was conducted in a central laboratory using a chromogenic FVIII assay. The pharmacokinetic parameters derived from a crossover study of Immunate in 18 previously treated patients older than 12 years of age are listed in the table below.

Summary of pharmacokinetic parameters for Immunate in 18 patients with severe Haemophilia A (Dose = 50 IU/kg):

Parameter				
	Mean	**SD**	**Median**	**90% CI**
AUC0-□ ([IUxh]/mL)	12.2	3.1	12.4	11.1 to 13.2
C_{max} (IU/mL)	1.0	0.3	0.9	0.8 to 1.0
T_{max} (h)	0.3	0.1	0.3	0.3 to 0.3
Terminal Half-Life (h)	12.7	3.2	12.2	10.8 to 15.3
Clearance (mL/h)	283	146	232	199 to 254
Mean residence time (h)	15.3	3.6	15.3	12.1 to 17.2

Parameter				
	Mean	**SD**	**Median**	**90% CI**
V_{ss} (mL)	4166	2021	3613	2815 to 4034
Incremental Recovery ([IU/mL]/[IU/kg])	0.020	0.006	0.019	0.016 to 0.020

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.

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.

5.3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

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

Solvent:

Sterilised Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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

24 months.

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.

6.4 Special precautions for storage

Store at 2 °C to 8 °C. Do not freeze. Store in the original package to protect from light.

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

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal and other handling

For reconstitution use only the administration set provided in the pack. Immunate is to be reconstituted immediately before administration as the preparation does not contain preservatives.

It is advisable to flush implanted venous access devices 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).

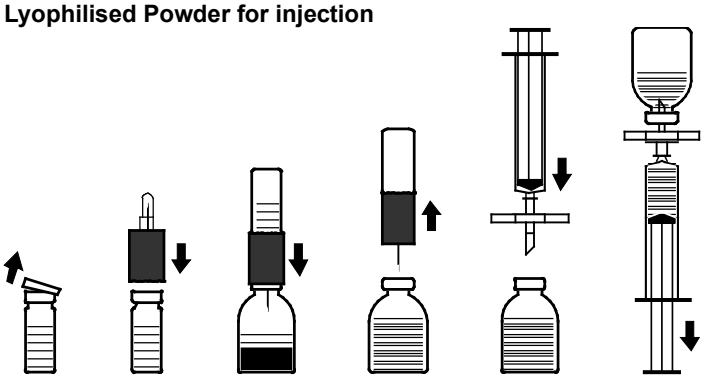


fig. A fig. B fig. C fig. D fig. E fig. F

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Takeda (Pty) Ltd

Building A

Monte Circle, Monte Casino Boulevard

Fourways 2191 Gauteng

South Africa

Tel: 011 514 3000

8 REGISTRATION NUMBER(S)

IMMUNATE 250 IU: A40/30.3/0215

IMMUNATE 500 IU: A40/30.3/0216

IMMUNATE 1000 IU: A40/30.3/0217

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first registration: 09 October 2009

10 DATE OF REVISION OF THE TEXT

27 April 2026