



Package leaflet: Information for the user

Immunate 250 IU powder and solvent for solution for injection

Active substances: Human Coagulation Factor VIII/ Human von Willebrand Factor

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Immunate is and what it is used for
2. What you need to know before you use Immunate
3. How to use Immunate
4. Possible side effects
5. How to store Immunate
6. Contents of the pack and other information

1. What Immunate is and what it is used for

What Immunate is

Immunate is a coagulation factor VIII / von Willebrand factor complex made from human plasma. The coagulation factor VIII in Immunate replaces the factor VIII which is lacking or is not functioning properly in haemophilia A. Haemophilia A is a sex-linked, hereditary blood coagulation defect due to reduced factor VIII levels. This results in severe bleeding in joints, muscles and inner organs, either spontaneously or as a consequence of accidental or surgical traumata. The administration of Immunate temporarily corrects the factor VIII deficiency and reduces the bleeding tendency.

In addition to its role as a Factor VIII protecting protein, von Willebrand Factor (VWF) mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation.

What Immunate is used for

Immunate is used for the treatment and prevention of bleeding in congenital (haemophilia A) or acquired factor VIII deficiency.

Immunate is also used for the treatment of bleeding in patients with von Willebrand's disease with factor VIII deficiency, if no specific preparation effective against von Willebrand's disease is available, and when desmopressin (DDAVP) treatment alone is ineffective or contraindicated.

2. What you need to know before you use Immunate

Do not use Immunate

If you are allergic to human coagulation factor VIII or any of the other ingredients of this medicine (listed in section 6).

If you are unsure about this, ask your doctor.

Warnings and precautions

When allergic reactions occur:

- There is a rare chance that you may experience an anaphylactic reaction (a severe, sudden allergic reaction) to Immunate. You should be aware of the early signs of allergic reactions such as flush, rash, hives, wheals, generalised itching, swelling of lips, eyelid and tongue, dyspnoea, wheezing, chest pain, tightness in the chest, general feeling of being unwell, dizziness, faster heart beat and low blood pressure. These symptoms can constitute an early symptom of an anaphylactic shock, manifestations of which may additionally include extreme dizziness, loss of consciousness, and extreme difficulty in breathing.
- If any of these symptoms occur, stop the injection/infusion immediately and contact your doctor. Severe symptoms, including difficulty in breathing and (near) fainting, require immediate emergency treatment.

When monitoring is required:

- Your doctor may wish to carry out tests to ensure that your current dose is sufficient to reach and maintain adequate factor VIII or von Willebrand levels.

When bleeding is still occurring:

- If your bleeding is not controlled with Immunate consult your doctor immediately.

You may have developed neutralizing antibodies (inhibitors) to factor VIII. Your doctor may wish to carry out tests to confirm this. Factor VIII inhibitors are antibodies in the blood that block the factor VIII you are using. This makes factor VIII less effective in controlling bleeding.

If you have von Willebrand's disease, especially type 3, you may develop neutralizing antibodies (inhibitors) to von Willebrand factor. Your doctor may wish to carry out tests to confirm this. Von Willebrand factor inhibitors are antibodies in the blood that block the von Willebrand factor you are using. This makes von Willebrand factor less effective in controlling bleeding.

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, the

testing of each donation and pools of plasma for signs of virus/infections, and the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B 19 infection may be serious for pregnant women (fetal infection) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia).

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived factor VIII products.

It is strongly recommended that every time you receive a dose of Immunate the name and batch number of the medicine are recorded in order to maintain a record of the batches used.

Immunate contains blood group isoagglutinins (anti-A and anti-B). If you have blood group A, B, or AB, haemolysis may occur following repetitive administration at short intervals or following administration of very large doses.

Children

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.

Other medicines and Immunate

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

No interactions of Immunate with other medicinal products have been reported.

Immunate must not be mixed with other medicinal products or solvents, except the enclosed Sterilised Water for Injections, prior to administration as this might impair the efficacy and safety of the product. It is advisable to flush implanted venous access with

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an appropriate solution, e.g. physiological saline solution, prior to and after infusion of Immunate.

Immunate with food and drink

There are no specific recommendations as to when Immunate should be administered with regard to meals.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There is no experience regarding the use of Immunate during pregnancy, breast-feeding and fertility as haemophilia A is rare in women. Immunate should be used during pregnancy and lactation only if clearly indicated. Therefore, inform your doctor if you are pregnant or breast-feeding. Your doctor will decide if Immunate may be used during pregnancy and lactation.

Driving and using machines

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

Immunate contains sodium

If you are on a low sodium diet, your doctor will monitor you with particular attention, as the quantity of sodium in the maximum daily dose may exceed 200 mg.

3. How to use Immunate

Your therapy should be under the supervision of a doctor experienced in the treatment of haemostatic disorders.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Dosage for prophylaxis of bleeding

If you are using Immunate to prevent bleeding (prophylaxis), your doctor will calculate the dose for you. He/she will do this according to your particular needs. The usual dose

will be between 20 to 40 IU factor VIII per kg of body weight, administered at intervals of 2 to 3 days. However, in some cases, especially in younger patients, shorter dose intervals or higher doses may be necessary.

If you have the impression that the effect of Immunate is insufficient, talk to your doctor.

Dosage for treatment of bleeding

If you are receiving Immunate for treatment of bleeding, your doctor will calculate the dose for you. He/she will do this according to your particular needs using the formula below:

$$\text{Required IU} = \text{body weight (kg)} \times \text{desired factor VIII rise (\% of normal)} \times 0.5$$

The following table is intended for your doctor only and provides a guide for dosing in bleeding episodes and surgery. In the case of the haemorrhagic events listed, the factor VIII activity should not fall below the given level (in % of normal) during the corresponding period.

Under certain circumstances, larger amounts than those calculated may be required, especially in the case of a low titre inhibitor.

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 infusions every 12 to 24 hours for 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 to 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		
<i>Minor</i> Including tooth extraction	30 - 60	Infusion every 24 hours, at least 1 day, until healing is achieved.

<i>Major</i>	80 – 100 (pre- and postoperative)	Repeat infusion every 8 to 24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a factor VIII activity of 30 % to 60 % (IU/dl).
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Monitoring by your doctor

Your doctor will perform appropriate laboratory tests to make sure that you have adequate factor VIII levels. This is particularly important if you are having major surgery.

Dosage in von Willebrand's disease

Replacement therapy with Immunate to control haemorrhages follows the guidelines given for haemophilia A.

Method and route of administration

Immunate is administered into a vein (intravenously) after preparing the solution with the solvent provided. Follow the directions given by your doctor closely.

The rate of administration should be determined by your comfort level and should not exceed 2 ml per minute.

Warm the product to room or body temperature prior to administration. For reconstitution use only the administration set provided in the pack because treatment failure can occur as a consequence of human coagulation factor VIII adsorption to the internal surfaces of some infusion equipment.

Immunate is to be reconstituted immediately before administration. The solution should then be used straight away as it does not contain preservatives. Reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear to slightly opalescent. Solutions that are turbid or have deposits are to be discarded. The ready-to-use solution must not be put back into the refrigerator.

Reconstitution of the powder to prepare a solution for injections:

Use aseptic technique!

1. Warm the unopened vial containing the solvent (sterilised water for injections) to room temperature (maximum 37°C).
2. Remove protective caps from the powder 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 powder vial and insert the free needle through the rubber stopper of the powder vial (fig. C). The solvent will be drawn into the powder vial by vacuum.
6. After approximately one minute, disconnect the two vials by removing the transfer set with the attached solvent vial from the powder 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 POWDER 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!

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).

Disconnect the syringe for a moment from the filter set. Air will enter into the powder vial and any foam will collapse. Then draw the solution into the syringe through the filter set (fig. F).

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).

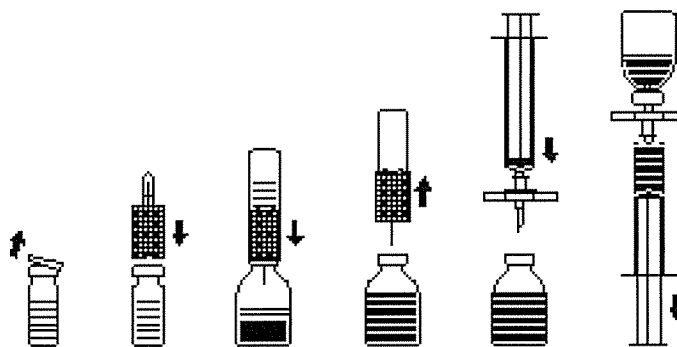


Fig. A Fig. B Fig. C Fig. D Fig. E Fig. F

Any unused product or waste material should be disposed of in accordance with local requirements.

The administration of Immunate should be documented, and the lot number recorded. A detachable documentation label is attached to each vial.

Frequency of administration

Your doctor will tell you how often and at what intervals Immunate is to be administered. He/she will do this according to the effectiveness in your individual case.

Duration of treatment

Usually, the replacement therapy with Immunate is life-long treatment.

If you use more Immunate than you should

- No symptoms of overdose with coagulation factor VIII have been reported. If you have any doubts, please consult your doctor.

- Thromboembolic events may occur.
- Hemolysis may occur in patients with blood group A, B, or AB.

If you forget to use Immunate

- Do not take a double dose to make up for a forgotten dose
- Proceed with the next regular administration immediately and continue at regular intervals as advised by your doctor.

If you stop using Immunate

Do not make a decision to stop using Immunate without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects possible with human plasma derived factor VIII products:

Allergic reactions, which may in some cases progress to severe and potentially life-threatening reactions (anaphylaxis), have been observed rarely. Therefore you should be aware of the early signs of allergic reactions such as flush, rash, hives, wheals, generalised itching, swelling of lips and tongue, dyspnoea, wheezing, tightness in the chest, low blood pressure, drop in blood pressure, general feeling of being unwell, and dizziness. These symptoms may be early signs of an anaphylactic shock. If allergic or anaphylactic reactions occur, stop the injection/infusion immediately and inform your doctor. Severe symptoms require immediate emergency treatment.

The formation of neutralising antibodies (inhibitors) to factor VIII or von Willebrand factor is a known complication in the treatment of patients with haemophilia A or von Willebrand's disease. If you develop neutralising antibodies (inhibitors), this can manifest itself as an insufficient clinical response (bleeding is not controlled with an appropriate dose) or as allergic reaction. In these cases it is recommended to contact a specialised haemophilia centre.

If you have blood group A, B or AB, haemolysis may occur following the administration of large doses.

Side effects reported with the use of Immunate:

The following frequencies are used to evaluate side effects:

very common:	may affect more than 1 in 10 people
common:	may affect up to 1 in 10 people
uncommon:	may affect up to 1 in 100 people
rare:	may affect up to 1 in 1,000 people
very rare:	may affect up to 1 in 10,000 people
not known:	frequency cannot be estimated from the available data

From the side effects listed in the table below, hypersensitivity has

been reported in a clinical trial, all other side effects were reported in post-marketing experience.

MedDRA Standard System Organ Class	Side Effect	Frequency
Immune system disorders	Hypersensitivity	Uncommon*
Blood and lymphatic system disorders	Factor VIII inhibition	Unknown
	Coagulation disorder	Unknown
Psychiatric disorders	Restlessness	Unknown
Nervous system disorders	Tingling or numbness	Unknown
	Dizziness	Unknown
	Headache	Unknown
Eye disorders	Conjunctivitis	Unknown
Cardiac disorders	Faster heart beat	Unknown
	Feeling your heartbeat	Unknown
Vascular disorders	Low blood pressure	Unknown
	Flushing	Unknown
	Pallor	Unknown
Respiratory, thoracic and mediastinal disorders	Shortness of breath	Unknown
	Cough	Unknown
Gastrointestinal disorders	Vomiting	Unknown
	Feeling sick	Unknown
Skin and subcutaneous tissue disorders	Hives	Unknown
	Rash	Unknown
	Itching	Unknown

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	Flush	Unknown
	Increased sweating	Unknown
	Neurodermatitis	Unknown
Musculoskeletal and connective tissue disorders	Muscle pain	Unknown
General disorders and administration site conditions	Chest pain	Unknown
	Chest discomfort	Unknown
	Oedema (including peripheral, eyelid and face oedema)	Unknown
	Fever	Unknown
	Chills	Unknown
	Injection site reactions (including burning)	Unknown
	Pain	Unknown

*one hypersensitivity reaction in 329 infusions in one clinical trial in 5 patients

Reporting of side effects:

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

5. How to store Immunate

Keep this medicine out of the sight and reach of children.

Store and transport refrigerated (2°C-8°C). Do not freeze.

Store in the original package in order to protect from light.

Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.

During the shelf life the product may be kept at room temperature (up to 25°C) for a single period not exceeding 6 months. Please record the beginning of storage at room temperature on the product carton. After storage at room temperature, Immunate must not be put back into the refrigerator but is to be used immediately or to be discarded.

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Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Immunate contains

Powder

- The active substances are human coagulation factor VIII and human von Willebrand factor. Each vial nominally contains 250 IU human coagulation factor VIII and 190 IU human plasma derived von Willebrand factor.
After reconstitution with the supplied solvent, the product contains approximately 50 IU/ml human plasma derived coagulation factor VIII and 38 IU/ml human plasma derived von Willebrand factor.
- The other ingredients are human albumin, glycine, sodium chloride, sodium citrate, lysine hydrochloride and calcium chloride.

Solvent

- Sterilised water for injections

What Immunate looks like and contents of the pack

Powder and solvent for solution for injection.

White or pale yellow powder or friable solid.

Both powder and solvent come in single dose glass vials, EP (powder: hydrolytic type II; solvent: hydrolytic type I) closed by butyl rubber stoppers, EP.

Each pack contains:

- 1 vial of Immunate 250 IU
- 1 vial with Sterilised Water for Injections (5 ml)
- 1 transfer/filter set
- 1 disposable syringe (5 ml)
- 1 disposable needle

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1 winged infusion set

Pack size: 1 x 250 IU

Manufacturer

Takeda Manufacturing Austria AG
Vienna, Austria

For any information about this medicine, please contact the local representative

Importer : Takeda (Thailand), Ltd., Bangkok, Thailand

This leaflet was last revised in January 2022