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Date: 16Jun2020		
OPTIONAL: Artwork Approver outside the Shire Management System:		Visible / Not Printed*: Dieline / Technical Info
Role:	**Name:** / **Signature:** / **Date:**	Takeda Confidential Property of Takeda

* Color not present in printed material.

Body Text Size: 9 pt

Code ITF 2/5	Datamatrix Code	RSS / GS1-128 Code
750095	NA	NA
Pharmacode	**Code 3 of 9**	**GTIN / EAN-13 Code**
NA	NA	NA

MedDRA Standard System Organ Class	Adverse Reaction	Frequency
	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 hæmophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients.

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.

4.9 Overdose
No case of overdose has been reported. Thrombœmbolic events may occur. See section 4.4.
Hemolysis may occur in patients with blood group A, B, or AB. See section 4.4.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic Group: anti-hæmorrhagics: von Willebrand factor and coagulation factor VIII in combination. ATC code: B02BD06.
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 hæmophiliac 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. Hæmophilia 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 results 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 factor VIII protecting protein, von Willebrand factor (VWF) mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation.

5.2 Pharmacokinetic properties
All pharmacokinetic parameters for Immunate were measured in subjects with severe Hemophilia 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 Hæmophilia A (Dose = 50 IU/kg):

Parameter	Mean	SD	Median	90% CI
$AUC_{0-\infty}$ ([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
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

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.
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, local tolerance and immunogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Powder:
Human albumin
Glycine
Sodium chloride
Sodium citrate
Lysine hydrochloride
Calcium chloride
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
2 years.
Chemical and physical in-use stability has been demonstrated for 3 hours at room temperature. From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination (controlled and validated aseptic conditions), the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Reconstituted product must not be returned to the refrigerator.
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 on the product package. At the end of this period the product must not be returned to the refrigerator but should be used immediately or discarded.

6.4 Special precautions for storage
Store and transport refrigerated (2°C – 8°C). Do not freeze.
Store in original package in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container
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 FVIII/190 IU VWF
1 vial with Sterilised Water for Injections (5 ml)
1 transfer/filter set
1 disposable syringe (5 ml)
1 disposable needle 1 winged infusion set
Pack size: 1 x 250 IU FVIII/190 IU VWF

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 dœs not contain preservatives.
Reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Solutions of reconstituted product that are turbid or have deposits must not be used.
It is advisable to flush implanted venous access devices with isotonic saline prior to and after infusion of Immunate.

Reconstitution of powder:
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 labelled potency will not be reduced.

Administration:
Use Aseptic Technique!
1. To prevent stopper-derived rubber particles from being administered with the medicinal product (risk of microœmbolism), 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 powder 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).

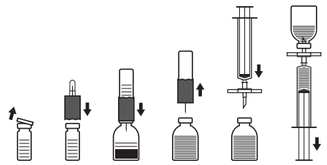

fig. A fig. B fig. C fig. D fig. E fig. F

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

7. MARKETING AUTHORISATION HOLDER
Takeda Malaysia Sdn. Bhd.
Unit TB-L13-1, Level 13, Tower B,
Plaza 33, No.1, Jalan Kemajuan,
Seksyen 13, 46200 Petaling Jaya,
Selangor Malaysia

Version number: 01
Reference: EU SmPC 11/2017
Date of local revision: 2 June 2020

IMMUNATE 50 IU/ML
POWDER AND SOLVENT FOR SOLUTION FOR INJECTION

Active Substances: Human coagulation Factor VIII/ Human von Willebrand Factor

0750095

1. NAME OF THE MEDICINAL PRODUCT
IMMUNATE 50 IU/ML POWDER AND SOLVENT FOR SOLUTION FOR INJECTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active Substances: Human coagulation Factor VIII/ Human von Willebrand Factor

Each vial contains nominally 250 IU human coagulation factor VIII1 and 190 IU human von Willebrand factor[2] (VWF:RCo).

Immunate 250 IU FVIII/190 IU VWF contains approximately 50 IU/ml of human coagulation factor VIII and 38 IU/ml human von Willebrand factor after reconstitution. The potency of factor VIII (IU) is determined using the European Pharmacopœia chromogenic assay. The specific activity of Immunate is 70 ± 30 IU FVIII/mg protein[3]. The potency of VWF (IU) is determined using the European Pharmacopœia ristocetin co-factor assay (VWF:RCo).

Produced from the plasma of human donors.

Excipients with known effect:

1 vial contains approx. 9.8 mg sodium.

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 hæmophilia A (congenital factor VIII deficiency, hæmophilia A with factor VIII inhibitor, acquired factor VIII deficiency due to spontaneous development of factor VIII inhibitor).

Von Willebrand's disease with factor VIII deficiency.

4.2 Posology and method of administration
Treatment should be under the supervision of a physician experienced in the treatment of hæmostatic disorders.

Posology

Dosage in Hæmophilia A
The dose 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 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 for 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 calculation of the required dose of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by approximately 2% of normal activity.

The required dose 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.

Hæmorrhages and Surgery

In the case of the following hæmorrhagic 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 hæmorrhage / Type of surgical procedure	Factor VIII level required (% of normal) (IU/dl)	Frequency of Doses (hours) / Duration of Therapy (days)
Hæmorrhage		
Early hæmarthrosis, 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.

[1] The FVIII potency was determined against the WHO International Standard for FVIII Concentrates.
[2] The ristocetin cofactor activity of human von Willebrand factor was determined against the WHO International Standard for von Willebrand Factor, Concentrate.
[3] without stabilizer (albumin); The maximum specific activity at a 1:1 ratio of factor VIII activity to von Willebrand factor-antigen is 100 IU factor VIII per mg protein.

Degree of hæmorrhage/ Type of surgical procedure	Factor VIII level required (% of normal) (IU/dl)	Frequency of Doses (hours) / Duration of Therapy (days)
Hæmorrhage		
More extensive hæmarthrosis, muscle bleeding or hæmatoma	30 – 60	Repeat infusion every 12 – 24 hours for 3 – 4 days or more until pain and acute disability are resolved
Life threatening hæmorrhages	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.
Major	80 – 100 (pre-and post- operative)	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, demonstrating different half- lives and recoveries.

Pædiatric 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 clinical data available for this patient group.

Long-term prophylaxis
For long term prophylaxis against bleeding in patients with severe hæmophilia 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.

Dosage in von Willebrand's disease
Replacement therapy with Immunate to control hæmorrhages follows the guidelines given for hæmophilia 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.
Method of administration
Intravenous use.
Immunate should be administered slowly via intravenous route. The maximal rate of infusion should not exceed 2 ml per minute.
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications
Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity
Allergic type hypersensitivity reactions are possible with Immunate. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, rash, flushing, pruritus, œdema (including face and eyelid œdema), tightness of the chest, wheezing, dyspnœa, chest pain, tachycardia, hypotension, and anaphylaxis up to allergic shock. In case of shock, standard medical treatment for shock should be implemented.

Patients with Hæmophilia A

Inhibitors
The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with hæmophilia 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 hæmophilia and factor VIII inhibitors.

Patients with von Willebrand's disease

Inhibitors
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.
As the quantity of sodium in the maximum daily dose may exceed 200 mg, it should be accounted for in people on a low sodium diet.
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 clinical data available for this patient group.
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.
The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A virus (HAV). The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. hæmolytic anæmia). Appropriate vaccination (hepatitis A and B) should be considered for patients in regular / repeated receipt of human plasma-derived factor VIII products.
It is strongly recommended that every time that Immunate is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.
Immunate contains blood group isoagglutinins (anti-A and anti-B). In patients with blood group A, B, or AB, hæmolysis may occur following repetitive administration at short intervals or following administration of very large doses.

4.5 Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed with Immunate.
No interactions of human coagulation factor VIII products with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation
Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of hæmophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, Immunate should be used during pregnancy and lactation only if clearly indicated.
See section 4.4 for information on parvovirus B19 infection. The effects of Immunate on fertility have not been established.

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 possible with human plasma derived factor VIII products:

Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angiœdema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, rash, headache, hives, pruritus, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, dyspnœa, 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 hæmophilia 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 hæmophilia centre be contacted.
Patients with von Willebrand disease, especially type 3 patients, may very rarely develop neutralising antibodies (inhibitors) to von Willebrand factor. If such inhibitors occur, the condition will manifest itself as an inadequate clinical response. Such antibodies may occur in close association with anaphylactic reactions. Therefore, patients experiencing anaphylactic reaction should be evaluated for the presence of an inhibitor. In all such cases, it is recommended that a specialised hæmophilia centre be contacted.
Hæmolysis may occur following administration of large doses to patients with blood group A, B or AB.
For safety information with respect to transmissible agents, see section 4.4.

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	Paræsthesia	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	Dyspnœa	Unknown
	Cough	Unknown
Gastrointestinal disorders	Vomiting	Unknown
	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 œdema)	Unknown
	Pyrexia	Unknown
	Chills	Unknown
	Injection site reactions (including burning)	Unknown