SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IMMUNINE 600 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: human coagulation factor IX

Each vial with powder for solution for injection contains nominally 600 IU human coagulation factor IX.

1 ml of solution of IMMUNINE contains approximately 120 IU/ml human coagulation factor IX, after reconstitution with 5 ml of Sterilised Water for injections.

The FIX potency (IU) is determined using the European Pharmacopoeia one-stage clotting test.

Produced from the plasma of human donors.

The specific activity of IMMUNINE is not less than 50 IU Factor IX / mg protein.

Excipient(s) with known effect

Sodium (20 mg per vial)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White or pale yellow lyophilised powder or friable solid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

IMMUNINE is indicated for all age groups from children older than 6 years to adults.
There is insufficient data to recommend the use of IMMUNINE in children less than 6 years of age.

4.2 Posology and method of administration

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

Posology
The dose and duration of the substitution therapy depend on the severity of the factor IX deficiency, the location and extent of bleeding and on the patient's clinical condition.

The number of units of factor IX administered is expressed in International Units (IU) which are related to the current WHO standard for factor IX products. Factor IX 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 IX concentrates in plasma).

One International Unit (IU) of factor IX activity is equivalent to that quantity of factor IX in one ml of normal human plasma.

On demand treatment
The calculation of the required dosage of factor IX is based on the empirical finding that 1 International Unit (IU) factor IX per kg body weight raises the plasma factor IX activity by 1.1% of normal activity in patients 12 years and older.

The required dose is determined using the following formula:

Required units = body weight (kg) x desired factor IX rise (%) (IU/dl) x 0.9

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. Factor IX products rarely require to be administered more than once daily.

In the case of the following haemorrhagic events, the factor IX activity should not fall below the given plasma activity level (in % of normal or in 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	**Factor IX level required (% of normal) (IU/dl)**	**Frequency of doses (hours)/ Duration of therapy (days)**
Haemorrhage		
Early hemarthrosis, muscle bleeding or oral bleeding	20-40	Repeat every 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 hematoma	30–60	Repeat infusion every 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.
Major surgery	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 FIX activity of 30% to 60%.

Prophylaxis
For long-term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are 20 to 40 IU of factor IX/kg body weight at intervals of 3 to 4 days.

In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

During the course of treatment, appropriate determination of factor IX 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 IX activity) is indispensable. Individual patients may vary in their response to factor IX, achieving different levels of *in vivo* recovery and demonstrating different half-lives.

Paediatric population
Available paediatric data is described in Section **"4.8 Undesirable effects"** under the new subsection "Special population" and in section "**5.2 Pharmacokinetic properties**".

Based on available clinical data recommendation on a posology for paediatric patients can be made for patients 12 to 18 years old. In the age group 6 years to 12 years the available clinical data are not sufficient for providing a dosage recommendation.

Method of administration
Intravenous use. It is recommended not to administer more than 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 substance or to any of the excipients listed in section 6.1.

- Known allergy to heparin or history of heparin induced thrombocytopenia.

Once these conditions have been checked through adequate treatment, IMMUNINE should only be administered to treat life-threatening bleeding.

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.

Hypersensitivity
Allergic type hypersensitivity reactions are possible with IMMUNINE. The product contains traces of human proteins other than factor IX.

If symptoms of hypersensitivity occur patients should be advised to discontinue use of the product immediately and contact their physician.

Patients and/or their caregivers should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. In case of shock, the current medical standards for shock treatment should be observed.

Inhibitors
After repeated treatment with human coagulation factor IX products, patients should be monitored for the development of ne0utralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

If the expected factor IX 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 IX inhibitor is present. In patients with high levels of inhibitor, factor IX 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 and therefore a specialised haemophilia centre should be contacted.

There have been reports in the literature showing an association between the occurrence of a factor IX inhibitor and allergic reactions**.** Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors might be at an increased risk of anaphylaxis with subsequent challenge with factor IX.

Because of the risk of allergic reactions with factor IX products, the initial administrations of factor IX should according to the treating physician's judgement be performed under medical observation where proper medical care for allergic reactions could be provided.

Thromboembolism, DIC, Fibrinolysis

Since the use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications, the risk being higher in low purity preparations, the use of factor IX-containing products may be potentially hazardous in patients with signs of fibrinolysis and in patients with disseminated intravascular coagulation (DIC).

Because of the potential risk of thrombotic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease, thrombophilia, hypercoagulability states, angina pectoris, coronary disease or acute myocardial infarction, to patients post-operatively, to premature new-borns or new-born infants, or to patients at risk of thrombotic phenomena or DIC. In each of these situations, the benefit of treatment with IMMUNINE should be weighed against the risk of these complications.

Viral Safety

- 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 red cell turnover (e.g. in haemolytic anaemia).
- Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma derived factor IX concentrates.

Precautions for Use

Sodium content

This medicinal product contains 20 mg sodium per vial, equivalent to 1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with IMMUNINE.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor IX. Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and breast-feeding is not available. Therefore, Factor IX should be used during pregnancy and lactation only if clearly indicated.

The effects of IMMUNINE on fertility have not been established.

With regard to the risk of Parvovirus B19 infection see warning statement under heading Viral Safety in section 4.4.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Summary of the safety profile
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 infrequently in patients treated with factor IX containing products.
In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors (see also section 4.4).

Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction.

On rare occasions fever has been observed.

Patients with haemophilia B may develop neutralising antibodies (inhibitors) to factor IX. (see section 4.4). 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 should be contacted.

There is a potential risk of thromboembolic episodes following the administration of factor IX products, with a higher risk for low purity preparations. The use of low purity factor IX products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high purity factor IX is rarely associated with such side effects.

For information on viral safety see section 4.4

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

The undesirable effects reported in the listings hereafter are based on reports from six clinical trials conducted with IMMUNINE in 197 subjects as well as from post marketing surveillance.

Frequencies have been evaluated according to the following convention: 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), not known (cannot be estimated from the available data).

MedDRA Standard System Organ Class	**Adverse Reactions**	**Frequency**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Factor IX inhibition	Not known
	Disseminated Intravascular Coagulation	Not known
IMMUNE SYSTEM DISORDERS	Allergic Reaction	Not known
	Anaphylactic Reactions/ Anaphylactoid Reactions	Not known
	Angiodema	Not known
	Hives	Not known
	In the presence of Inhibitors: Serum Sickness	Not known
	Hypersensitivity Reaction	Not known
NERVOUS SYSTEM DISORDERS	Headache	Not known
	Restlessness	Not known
	Tingling	Not known
CARDIAC DISORDERS	Myocardial Infarction	Not known
	Tachycardia	Not known
VASCULAR DISORDERS	Hypotension	Not known
	Thromboembolic Episodes (e.g. Pulmonary Embolism, Venous Thrombosis, Arterial Thrombosis, Cerebral Artery Thrombosis)	Not known
	Flushing	Not known
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Throat Irritation	Uncommon
	Oropharyngeal Pain	Uncommon
	Cough (dry)	Uncommon
	Wheezing	Not known
	Dyspnea	Not known
GASTROINTESTINAL DISORDER	Nausea	Not known
	Vomiting	Not known
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash	Uncommon
	Pruritus	Uncommon
	Urticaria	Not known

MedDRA Standard System Organ Class	Adverse Reactions	Frequency
RENAL AND URINARY DISORDERS	Nephrotic Syndrome[1]	Not known
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Pyrexia	Uncommon
	Chills	Not known
	Burning and stinging at infusion site	Not known
	Lethargy	Not known
	Chest tightness	Not known

Inhibitors to factor IX
In clinical trials with IMMUNINE no factor IX inhibitors were identified. No previously untreated patients (PUPs) were enrolled in IMMUNINE clinical trials.

Special population
The use of IMMUNINE was investigated in paediatric patients in patient groups 6 to 12 years and above 12 years of age with Haemophilia B. The safety was similar to the safety in adults using IMMUNINE.

Furthermore, the use of IMMUNINE was investigated in two observational studies also in children of up to 6 years of age and patients 0-64 years old with Haemophilia B, respectively. The safety in children up to 6 years was similar to that in children above 6 years and in adults using IMMUNINE.

Possible undesirable effects with human coagulation factor IX concentrates: Paraesthesia

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics: blood coagulation factor IX.
ATC code: B02BD04

Factor IX is a single chain glycoprotein with a molecular mass of about 68,000 Dalton. It is a vitamin-K dependent coagulation factor and it is synthesised in the liver. Factor IX is activated by factor XIa in the intrinsic coagulation pathway and by the factor VII/tissue factor complex in the extrinsic pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot is formed. Haemophilia B is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor IX and results in profuse bleeding into joints, muscles or internal organs, either

[1] following attempted immune tolerance induction

spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor IX is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Paediatric population
There is insufficient data to recommend the use of IMMUNINE in children less than 6 years of age.

5.2 Pharmacokinetic properties

Based on a phase 4 study the mean incremental recovery (IR) of FIX in previously treated patients (PTPs) 12 years and older (n=27) was 1.1 (±0.27) ranging from 0.6 to 1.7 IU/dL per IU/kg. In the same study the mean IR in PTPs 11 years and younger (n=4) was 0.9 (± 0.12) ranging from 0.8 to 1.1.

A pharmacokinetic study with 26 patients yielded the following results:

Parameter	Number	Mean value	SD	95%CI
Clearance (ml/h/kg)	26	8.89	2.91	7.72-10.06
Mean residual time (h)	26	23.86	5.09	1.85-25.88

The biological half-life is approximately 17 hours.

5.3 Preclinical safety data

IMMUNINE is a highly purified factor IX concentrate containing only traces of factor II, VII and X. Single dose administration of IMMUNINE to laboratory animals revealed no signs for toxicological or thrombogenic potential.

Non-clinical studies with repeated dose administration are not meaningful to perform due to the heterologous character of human proteins in laboratory animals.

Since factor IX is a protein of human origin, which, under physiological conditions, circulates in the plasma neither toxic effects on reproduction, nor mutagenic and carcinogenic effects are to be expected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: Sodium chloride
Sodium citrate dihydrate

Solvent: Sterilised Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Only the provided injection/infusion sets should be used because treatment failure can occur as a consequence of human coagulation factor IX adsorption to the internal surfaces of some injection/infusion equipment.

6.3 Shelf life

2 years

Chemical and physical in-use stability of reconstituted IMMUNINE has been demonstrated for 3 hours at temperatures up to 25°C. From a microbiological point of view the product should be used immediately unless the method of reconstitution precludes the risk of microbial contamination (validated aseptical environment). If not used immediately, in use-storage and conditions is the responsibility of the user. Reconstituted product must not be returned to the refrigerator.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

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

Within the indicated shelf life, IMMUNINE may be stored at room temperature (up to 25°C) for a period of 3 months. Record this period of storage on the product package. After the end of this period, IMMUNINE must not be returned to the refrigerator, but should be used immediately or discarded.

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

6.5 Nature and contents of container

IMMUNINE powder comes in single dose vials of neutral glass of hydrolytic type II. The solvent comes in single dose vials of neutral glass of hydrolytic type I. The product vials are closed with chlorobutyl rubber stoppers. The solvent vials are closed with chlorobutyl or bromobutyl rubber stoppers.

Contents of the container:
1 vial IMMUNINE 600 IU
1 vial 5 ml Sterilised Water for Injections
1 transfer needle
1 aeration needle
1 filter needle
1 disposable needle
1 disposable syringe (5 ml)
1 infusion set

Pack size: 1 x 600 IU

6.6 Special precautions for disposal and other handling

Only the provided injection/infusion sets should be used.

IMMUNINE is to be reconstituted only immediately before administration. The solution should then be used promptly (preparation does not contain any preservatives). Infusion has to be completed within 3 hours after reconstitution. See section 6.4 Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

It is advisable to rinse a common venous access with isotonic saline prior to and after infusion of IMMUNINE.

Reconstitution of powder to prepare a solution for injection:

Use aseptic technique!

1. Warm the unopened vial containing solvent (Sterilised Water for Injections) to room temperature (max. +37°C).
2. Remove protective caps from the powder vial and solvent vial (fig. A) and disinfect the rubber stoppers of both.
3. Remove protective covering from one end of the enclosed transfer needle by twisting and pulling. Insert the exposed needle through the rubber stopper of the solvent vial (fig. B and C).
4. Remove protective covering from the other end of the transfer needle taking care not to touch the exposed end.
5. Invert the solvent vial over the powder vial and insert the free end of the transfer needle through the rubber stopper of the powder vial (fig. D). The solvent will be drawn into the powder vial by vacuum.
6. Disconnect the two vials by removing the needle from the powder vial (fig. E). Gently agitate or rotate the powder vial to accelerate dissolution.
7. Upon complete reconstitution of the powder, insert the enclosed aeration needle (fig. F) and any foam will collapse. Remove aeration needle.

Injection/Infusion:

Use aseptic technique!

1. Remove protective covering from the enclosed filter needle by twisting and pulling and fit the needle onto a sterile disposable syringe. Draw the solution into the syringe (fig. G).
2. Disconnect the filter needle from the syringe and slowly inject the solution intravenously (maximum rate of injection 2 ml/min) with the enclosed winged infusion set (or the enclosed disposable needle).

If administered by infusion, a disposable infusion set with adequate filter is to be used.

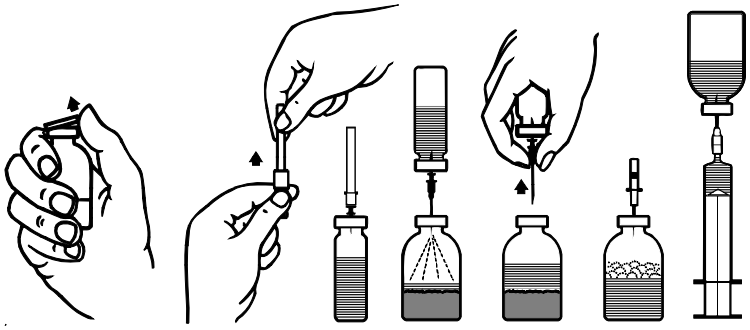

fig. A fig. B fig. C fig. D fig. E fig. F fig. G

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

7. MARKETING AUTHORISATION HOLDER

Takeda (Thailand), Ltd., Bangkok, Thailand

8. MANUFACTURER

Takeda Manufacturing Austria AG, Vienna, Austria

9. MARKETING AUTHORISATION NUMBER(S)

Reg.no. 1C 3/63 (B)

10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 January 2020

11. DATE OF REVISION OF THE TEXT

28 November 2023