

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Immunine 200 IU powder and solvent for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: human coagulation factor IX.

1 vial with powder for solution for injection contains 200 IU human coagulation factor IX.

1 ml of solution contains approximately 40 IU/ml human coagulation factor IX, when reconstituted with 5 ml of Sterilised Water for injections.

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

Specific activity of IMMUNINE is ≥ 50 IU Factor IX per mg protein.

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection or infusion.

White or pale yellow lyophilised powder or friable solid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Immunine is indicated for all age groups from children elder than 6 years to adults.

There are 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 hemophilia.

Posology

The dosage and duration of the substitution therapy depend on the severity of the factor IX deficiency, on 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.

The calculation of the required dosage of factor IX is based on the empirical finding that 1 IU factor IX per kg body weight raises the plasma factor IX activity by 0.9% of normal activity.

The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor IX rise (%) (IU/dl) x 1.1

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 hemorrhagic 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 hemorrhage/ Type of surgical procedure	Factor IX level required (% of normal or in IU/dl)	Frequency of doses (hours)/ Duration of therapy (days)
Hemorrhage		
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 hemarthrosis, 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 hemorrhages	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 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%.

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.

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

Patients should be monitored for the development of factor IX inhibitors. 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 hemophilia. See also section 4.4.

Paediatric population

There are insufficient data to recommend the use of IMMUNINE in children less than 6 years of age. Therefore, no recommendation on a posology can be made.

Method of administration

The product should be administered via the intravenous route. 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.

Disseminated intravascular coagulation (DIC) and/or hyperfibrinolysis.

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

As with any intravenous protein product, allergic type hypersensitivity reactions are possible.

The product contains traces of human proteins other than factor IX. 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 case of shock, the current medical standards for shock treatment should be observed.

Patients with a risk of thrombosis (e.g. patients with a history of liver disease, thrombophilia, hypercoagulability states, angina pectoris, coronary disease or acute myocardial infarction or in premature newborns) should be carefully monitored for the development of DIC and/or thrombosis. In patients with suspected DIC, replacement therapy should be stopped immediately.

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 HIV, HBV and HCV and for the non-enveloped 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 hemolytic anemia).

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma derived factor IX concentrates.

It is strongly recommended that every time that IMMUNINE 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.

Immunine 200 IU contains the calculated value of 20 mg sodium per vial. This is to be taken into consideration in patients on a low-sodium diet.

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

There have been reports in the literature showing a correlation 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 concentrates, 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.

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, to patients post-operatively, to newborn 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.

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 hemophilia 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.

4.7 Effects on ability to drive and use machines

Immunine has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The undesirable effects reported in the listings hereafter are based on reports from clinical trials and from post marketing surveillance.

Their frequency has been evaluated by using the following criteria: very common ($\geq 1/10$) common ($\geq 1/100$; $< 1/10$), uncommon ($\geq 1/1,000$; $< 1/100$), rare ($\geq 1/10,000$; $< 1/1,000$) and very rare ($< 1/10,000$)

Reports from clinical trials

The following undesirable effects are categorised as uncommon (incidence rate $\geq 1/1,000$; $< 1/100$).

Skin and subcutaneous tissue disorders

Itching

Rash

Respiratory, thoracic and mediastinal disorders

Tingling throat/Sore throat

Dry cough

Reports from Post Marketing Surveillance

The following undesirable effects are categorised as very rare (incidence rate $< 1/10,000$).

Blood and lymphatic system disorder

- Neutralising antibodies (inhibitors) to factor IX,
- Disseminated Intravascular Coagulation

Immune System Disorders

- Allergic reactions,
- Severe anaphylaxis,
- Angiodema,
- Flushing,
- Generalised Urticaria,
- Hives

Nervous System Disorders

- Headache,
- Restlessness,
- Tingling

Cardiac Disorders

- Tachycardia,
- Myocardial Infarction

Vascular Disorders

- Hypotension,
- Thromboembolic Episodes,
- Pulmonary embolism,
- Venous thrombosis

Respiratory, Thoracic and Mediastinal Disorders

- Wheezing

Gastrointestinal Disorders

- Nausea,
- Vomiting

Skin and Subcutaneous Tissue Disorders

- Rash

Renal and Urinary Disorders

- Nephrotic Syndrome

General Disorders and Administration Site Condition

- Chills,
- Burning and Stinging at infusion site,
- Fever,
- Hypersensitivity reactions,
- Lethargy,
- Tightness of the chest

Possible undesirable effects with human coagulation factor IX concentrates:

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 hemophilia B patients with factor IX inhibitors and a history of allergic reaction.

On rare occasions fever has been observed.

Patients with hemophilia B may develop neutralising antibodies (inhibitors) to factor IX. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised hemophilia centre 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.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics: 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. Hemophilia 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 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 are insufficient data to recommend the use of IMMUNINE in children less than 6 years of age.

5.2 Pharmacokinetic properties

The in vivo recovery of factor IX is 0.92 ± 0.06 IU/dl per IU/kg administered (approximately 40%), and the biological half-life is approximately 17 hours. After i.v. administration, the peak concentration is reached after 10 to 30 minutes.

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

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 bromobutyl rubber stoppers.

Contents of the container:

1 vial IMMUNINE 200 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 sizes: 1 x 200 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). The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.

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.

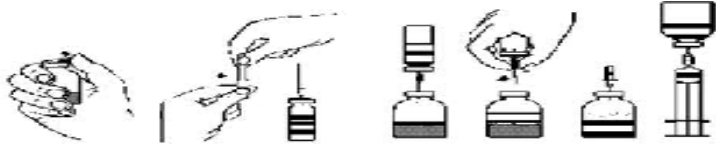


fig. A fig. B fig. C fig. D fig. E fig. F fig. G

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

7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Limited
Caxton Way
Thetford
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8 MARKETING AUTHORISATION NUMBER

PA 167/132/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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