

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Immunine 1200 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 1200 IU human coagulation factor IX.

1 ml of solution contains approximately 120 IU/ml human coagulation factor IX, when reconstituted with 10 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  $\geq 50$  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, 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)
<b>Hemorrhage</b>		
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.
<b>Surgery</b>		
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.

#### Inhibitor Development

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.
- 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

#### Hypersensitivity reactions

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. The product contains traces of human proteins other than factor IX. 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. If these symptoms occur, they should be advised to discontinue use of the product immediately and contact their physician.

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 concentrates, the initial administrations of factor IX should according to the treating physician's judgement be performed under medical observation where proper immediate medical care for allergic/anaphylactic reactions could be provided.

In case of shock, the current medical standards for shock treatment should be observed.

#### 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 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.

#### Development of Inhibitors

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.

In case of inhibitor development a specialised haemophilia center should be contacted.

#### 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 newborns or 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.

In patients with suspected DIC, replacement with IMMUNINE should be stopped immediately.

## Precautions for Use

### Sodium content

Immunine 1200 IU contains the calculated value of 41 mg sodium per vial. This is to be taken into consideration in patients on a low-sodium diet.

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.

## 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.

See section 4.4. 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 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. (see Section 4.4). In such

cases, it is recommended that a specialised haemophilia centre should be contacted. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response.

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 undesirable effects reported in the listings hereafter are based on reports from clinical trials conducted with IMMUNINE in 148 subjects administered 2807 infusions as well as from post marketing surveillance.

The frequency of adverse reactions 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 ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

The following adverse reactions are listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity, where feasible.

<b>System organ class according to the MedDRA data bank</b>	<b>Undesirable effect</b>	<b>Frequency</b>
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Inhibitor Development	Not known
	Disseminated Intravascular Coagulation	Not known
IMMUNE SYSTEM DISORDERS	Allergic reaction	Not known
	Anaphylactic reaction	Not known
	Angiodema	Not known
	Hives	Not known
	<u>Occurred with Inhibitors</u>	
	Serum Sickness Hypersensitivity Reaction	Not known 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	Not known
	Pulmonary Embolism	Not known
	Venous Thrombosis	Not known
	Flushing	Not known
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Throat Irritation	Uncommon
	Oropharyngeal Pain	Rare
	Cough Dry	Rare
	Wheezing	Not known
	Dyspnea	Not known

GASTROINTESTINAL DISORDER	Nausea	Not known
	Vomiting	Not known
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash	Uncommon
	Pruritus	Rare
	Urticaria	Not known
RENAL AND URINARY DISORDERS	Nephrotic Syndrome	Not known
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Pyrexia	Rare
	Chills	Not known
	Burning and stinging at infusion site	Not known
	Lethargy	Not known
	Tightness of the chest	Not known

**Possible undesirable effects with human coagulation factor IX concentrates:** Paresthesia

## 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.

### 5.2 Pharmacokinetic properties

The in vivo recovery of factor IX is  $0.92 \pm 0.06$  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

Paediatric population

Data available in children less than 6 years of age are limited.

### 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/or below 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 aseptic 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 the 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 1200 IU
- 1 vial 10 ml Sterilised Water for Injections
- 1 transfer needle
- 1 aeration needle
- 1 filter needle
- 1 disposable needle
- 1 disposable syringe (10 ml)
- 1 infusion set

Pack sizes: 1 x 1200 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.

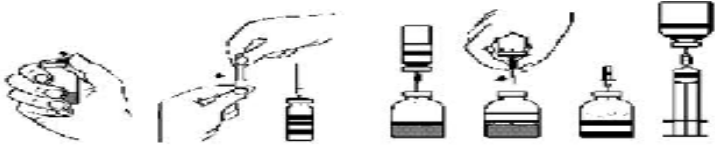


fig. A    fig. B    fig. C    fig. D    fig. E    fig. F    fig. G

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  
Norfolk  
IP24 3SE  
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## **8 MARKETING AUTHORISATION NUMBER**

PA 167/132/3

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 14th March 2008

Date of last renewal: 15th March 2011

## **10 DATE OF REVISION OF THE TEXT**

April 2012