IMMUNINE

Purified Factor IX Concentrate
Virus-Inactivated

Baxter

QUALITATIVE AND QUANTITATIVE COMPOSITION

IMMUNINE	200 IU	600 IU	1200 IU
active ingredient blood coagulation factor IX			
potency	200 IU[1]	600 IU[1]	1200 IU[1]
specific activity	100 ± 50 IU/mg protein		
other ingredients			
trisodium citrate·2H_2O	20 mg	20 mg	40 mg
sodium chloride	40 mg	40 mg	80 mg
sterilised water for injections	5 ml	5 ml	10 ml

PHARMACEUTICAL FORM

The product is presented as freeze-dried powder accompanied by the appropriate volume of solvent for solution for injection. The reconstituted solution is intended for intravenous administration.

PHARMACOTHERAPEUTIC GROUP

Antihemorrhagics: blood coagulation factor IX.

ATC code: B02BD04

MANUFACTURER

Baxter AG, Vienna, Austria

THERAPEUTIC INDICATIONS

Treatment and prophylaxis of bleeding episodes caused by congenital or acquired factor IX deficiency (hemophilia B, hemophilia B with factor IX inhibitor, acquired factor IX deficiency due to spontaneous development of factor IX inhibitor).

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.

SPECIAL WARNINGS AND SPECIAL 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.

In 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) the factor IX level should not be raised beyond 60% of normal. In addition, these patients – as well as patients receiving high doses of human blood coagulation factor IX concentrate for major surgery – should be monitored for the development of DIC and/or thrombosis. In patients with suspected DIC, replacement therapy should be stopped immediately.

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of unknown nature. The risk of transmission of infective agents is however reduced by:

- selection of donors by a medical interview and screening of individual donations and plasma pools for HB_SAg and antibodies to HIV and HCV.
- testing of plasma pools for genomic material of HCV, HBV and HIV-1 and -2.
- inactivation/removal procedures included in the production process that have been validated using model viruses. These procedures are considered effective for HIV, HCV, HAV and HBV.

Appropriate vaccination (hepatitis A and B) for patients in receipt of plasma derived factor IX concentrates is recommended.

The viral inactivation/removal procedures may be of limited value against non-enveloped viruses such as parvovirus B19.

Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased red cell production (e.g. in hemolytic anaemia).

As the quantity of sodium in the maximum daily dose may exceed 200 mg, it may be harmful to people 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.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

No interactions of human coagulation factor IX products with other medicinal products are known.

As for any blood coagulation factor concentrate, IMMUNINE should not be mixed with other medicinal products before administration, as this might impair the efficacy and safety of the product.

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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

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).

One International Unit (IU) of factor IX activity is equivalent to that quantity of factor IX in 1 ml of normal human plasma.

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 0.8% of normal activity.

The required dosage is determined using the following formula:

$$\text{Required units} = \text{body weight (kg)} \times \text{desired factor IX rise (\%)} \times 1.2$$

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 the corresponding period.

[1] The F IX potency was determined using an in vitro one-stage clotting assay calibrated against the World Health Organization (WHO) International Standard for F IX Concentrates.

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)	Frequency of doses (hours)/Duration of therapy (days)
Hemorrhage		
Early hemarthrosis, muscle bleed 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 such as head surgery, throat bleeding, severe abdominal bleeding	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 F IX activity of 30% to 60%.

Under certain circumstances larger amounts than those calculated may be required, especially in the case of the initial dose.

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/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.

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

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 "Special Warnings and Special Precautions".

If the inhibitor is present at levels less than 10 Bethesda Units (BU) per ml, administration of additional human coagulation factor IX may neutralize the inhibitor. In patients with inhibitor titers above 10 BU or with high anamnestic response, the use of (activated) prothrombin complex concentrate (PCC or aPCC) or recombinant activated factor VII (rFVIIa) preparations has to be considered. These therapies should be directed by physicians with experience in the care of patients with hemophilia.

Method of administration

IMMUNINE is to be reconstituted only immediately before administration. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. The solution should then be used promptly (preparation does not contain any preservatives). Any unused solution must be disposed of appropriately. Inject or infuse slowly intravenously. It is recommended not to administer more than 2 ml per minute.

Reconstitution of dried substance

1. Warm the unopened vial containing solvent (Sterilised Water for Injections) to room temperature (max. +37°C).
2. Remove protective caps from the concentrate 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 (fig. B). Insert the exposed needle through the rubber stopper of the solvent vial (fig. 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 concentrate vial, and insert the free end of the transfer needle through the rubber stopper of the concentrate vial (fig. D). The solvent will be drawn into the concentrate vial by vacuum.
6. Disconnect the two vials by removing the needle from the concentrate vial (fig. E). Gently agitate or rotate the concentrate vial to accelerate dissolution.
7. Upon complete reconstitution of the concentrate, insert the enclosed "aeration needle" (fig. F) and any foam will collapse. Remove aeration needle.

Injection

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).

Infusion

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

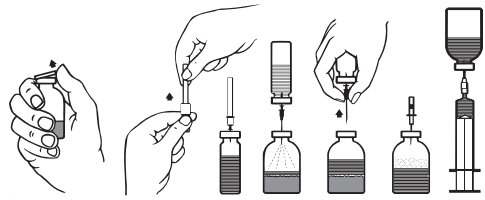

fig. A fig. B fig. C fig. D fig. E fig. F fig. G

UNDESIRABLE EFFECTS

Hypersensitivity or allergic reactions (which may include angiodema, 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 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 reactions.

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 limited experience to date of treatment with IMMUNINE in previously untreated patients.

There is a potential risk of thromboembolic episodes following the administration of factor IX product, 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.

OVERDOSE

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

INCOMPATIBILITIES

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.

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

SHELF LIFE AND STORAGE

Store between +2°C and +8°C. IMMUNINE must not be used beyond the expiration date indicated on each pack.

Within the indicated shelf life, IMMUNINE may be stored at room temperature (+25°C) for a period of 3 months. Record the period of storage at room temperature below the expiration date indicated on the product package.

Chemical and physical in-use stability of reconstituted IMMUNINE has been demonstrated for 6 hours at room temperature. From the microbiological point of view the product should be used immediately unless the method of reconstitution precludes the risk of microbial contamination. If not used immediately, in use-storage and conditions is the responsibility of the user. Reconstituted product must not be returned to the refrigerator.

Store out of the reach of children.