

BEBULIN

(Factor IX Complex), Nanofiltered and Vapor Heated

DESCRIPTION

BEBULIN (Factor IX Complex), Nanofiltered and Vapor Heated is a purified, sterile, stable, freeze-dried concentrate of the Coagulation Factor IX (Christmas Factor) as well as Factor II (Prothrombin) and Factor X (Stuart-Prower Factor) and low amounts of Factor VII. In addition, the product contains small amounts of heparin (≤ 0.15 IU heparin per IU Factor IX).

BEBULIN is standardized in terms of Factor IX content and each vial is labeled for the Factor IX content indicated in International Units (IU). One International Unit of Factor IX (according to the current International Standard for Human Blood Coagulation Factors II, IX, and X in Concentrates) corresponds to the activity of Factor IX in 1 mL of fresh normal human plasma.

BEBULIN is manufactured from large plasma pools of human plasma. Screening against potentially infectious agents begins with the donor selection process and continues throughout plasma collection and plasma preparation. Each individual plasma donation used in the manufacture of BEBULIN is collected only at FDA approved blood establishments and is tested by FDA licensed serological tests for Hepatitis B Surface Antigen (HBsAg), and for antibodies to Human Immunodeficiency Virus (HIV-1/HIV-2) and Hepatitis C Virus (HCV) in accordance with U.S. regulatory requirements. As an additional safety measure, mini-pools of the plasma are tested for the presence of HIV-1 and HCV by FDA licensed Nucleic Acid Testing (NAT) and found negative. In addition, two dedicated and independent virus removal/inactivation steps have been integrated into the manufacturing process, namely 35 nm nanofiltration¹ and a vapor heat treatment process² [10 hours at 60 °C and subsequent 1 hour at 80 °C under the condition of 7-8% (w/v) residual moisture]. In addition, the DEAE-Sephadex adsorption contributes to the virus safety profile of BEBULIN. Despite these measures, such products can still potentially transmit disease (see WARNINGS).

In vitro spiking studies have been used to validate the capability of the manufacturing process to remove and inactivate viruses. To establish virus clearance capacity of the manufacturing process, these virus clearance studies were performed in accordance with good laboratory practices under extreme conditions (e.g. at minimum incubation times and temperatures below specifications for vapor-heat treatment). The *in vitro* viral reduction studies performed on nanofiltered BEBULIN are summarized in Table 1.

Table 1
Mean log₁₀ Reduction Factors (RFs) For Each Virus and Manufacturing Step*

Virus Type	Enveloped RNA		Enveloped DNA	Non-enveloped RNA	Non-enveloped DNA
	Retroviridae	Flaviviridae	Herpesviridae	Picornaviridae	Parvoviridae**
Virus*	HIV-1	BVDV	PRV	HAV	MMV
DEAE Sephadex Adsorption	n.d.	n.d.	n.d.	1.4	1.3
35 nm Nanofiltration ¹	> 6.4	2.0	> 6.0	1.7	≤ 1.0
Vapor-Heat Treatment	> 6.8	> 7.1	> 7.4	> 4.5	≤ 1.0
Overall log reduction factor (ORF)	> 13.2	> 9.1	> 13.4	> 7.6	1.3

n.d.: Not done

* Reduction factors < 1 log are not used for calculation of the overall reduction factor.

HIV-1: Human Immunodeficiency Virus Type 1

BVDV: Bovine Viral Diarrhea Virus (model for Hepatitis C Virus and other lipid enveloped RNA viruses)

PRV: Pseudorabies Virus (model for lipid enveloped DNA viruses including Hepatitis B Virus)

HAV: Hepatitis A Virus

MMV: Mice Minute Virus (model for non-lipid enveloped DNA viruses, including human parvovirus B19 [B19V])

** Studies on B19V, which are considered experimental in nature, have demonstrated a virus reduction factor of not more than 3.6 log₁₀ and 4.6 log₁₀ by DEAE-Sephadex adsorption and vapor-heat treatment, respectively.

† Studies on West Nile Virus (WNV), have demonstrated a virus reduction factor of 3.1 log₁₀ by the 35 nm nanofiltration step.

CLINICAL PHARMACOLOGY

BEBULIN is a combination of vitamin K-dependent clotting factors found in normal plasma. The administration of BEBULIN provides an increase in plasma levels of Factor IX and can temporarily correct the coagulation defect of patients with Factor IX deficiency. Plasma levels of Factors II and X will also be increased. However, no clinical studies have been conducted to show benefit from this product for treating deficiencies other than Factor IX deficiency.

In vivo recovery of BEBULIN was determined by investigators in Germany, Japan, and the United States using the former International Standard, WHO 72/32 and was found to be 53.3% \pm 9.6%, 57.5% \pm 21.8%, and 53.24% \pm 16.95%, respectively. In the same studies, using different methodologies, half-lives were determined to be 19.4 hrs \pm 3.8 hrs, 24.6 hrs \pm 3.2 hrs, and 19.97 hrs \pm 8.24 hrs, respectively.¹

In the context of two prospective clinical studies and a retrospective survey, BEBULIN was followed up for the risk of transfusion-transmitted viral infections. All patients received blood products for the first time. Using criteria established by the ICTH, 16 patients were followed up for non-A, non-B hepatitis, 9 for HCV seroconversion, 3 for hepatitis B, and 24 for HIV seroconversion. None tested positive for any of these infections. Additional 3 patients with 2 or more consecutive test samples missing tested negative for non-A, non-B hepatitis for all samples available.

INDICATIONS AND USAGE

BEBULIN is indicated for the prevention and control of hemorrhagic episodes in hemophilia B patients.

BEBULIN is not indicated for use in the treatment of Factor VII deficiency. No clinical studies have been conducted to show benefit from this product for treating deficiencies other than Factor IX deficiency.

CONTRAINDICATIONS

None known.

WARNINGS

Thromboembolic Complications

The risk of thromboembolic complications including disseminated intravascular coagulation (DIC) and hyperfibrinolysis is present with the administration of Factor IX Complex, particularly in the postoperative period and in patients with risk factors predisposing to thrombosis.

Transmission of Infectious Agents

BEBULIN is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by effective donor screening, testing for the presence of certain current virus infections, by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g. viruses, and theoretically, the Creutzfeldt-Jacob disease (CJD) agent. ALL adverse reactions including infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Baxter Healthcare Corporation at 1-800-423-2862 (in the U.S.) and FDA Med Watch (1-800-FDA-1088 or www.fda.gov/medwatch). The physician should discuss the risks and benefits of this product with the patient.

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly non-A, non-B hepatitis. Hepatitis B vaccination is essential for patients with hemophilia and it is recommended that this be done at birth or diagnosis.

PRECAUTIONS

Severe hypotensive reaction, such as anaphylactic shock, requires immediate intervention using current principles of shock therapy. Have epinephrine available for immediate administration, if appropriate, in the event of an anaphylactic reaction to BEBULIN.

In patients with risk factors predisposing to thrombosis, do not raise the Factor IX level to more than approximately 60% of normal.⁴ The risk factor for thromboembolic complications include, but are not limited to, patients with a history of coronary heart disease, liver disease, disseminated intravascular coagulation, post-operative immobilization, elderly patients and neonates. Monitor such patients, as well as patients who require high doses of Factor IX because of major surgical interventions, for the possible development of DIC and/or thrombosis. Stop treatment immediately in case changes occur in blood pressure or pulse rate or symptoms such as respiratory distress, chest pain or cough.

Information for Patients

Some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 most seriously affects pregnant women or immune-compromised individuals. Symptoms of parvovirus B19 infection include fever, drowsiness, chills, and runny nose followed about two weeks later by a rash, and joint pain.

Inform patients of signs and symptoms of immediate hypersensitivity reactions such as fever, urticaria/hives, rashes, nausea, retching, angioedema/swelling of face or other body areas, laryngeal edema, stridor, dysphonia, bronchospasm/wheezing, hypotension, dizziness, lightheadedness, or loss of consciousness. Advise patients to discontinue use of the product and contact their physician if these symptoms occur. Patients should seek emergency care immediately for serious symptoms.

Pregnancy Category C

Animal reproduction studies have not been conducted with BEBULIN. It is also not known whether BEBULIN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. BEBULIN should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Anaphylactoid or anaphylactic reactions may occur following infusion of BEBULIN. The occurrence of these reactions (e.g. fever, urticarial rashes, nausea, retching, dyspnea, anaphylactic shock) necessitates the interruption of replacement therapy. Mild reactions (transient discomfort that resolves spontaneously or with minimal intervention), such as rash, can be managed with antihistamines.

DOSAGE AND ADMINISTRATION

General

For intravenous administration only

As a general rule, 1 International Unit of Factor IX activity/kg will increase the plasma level of Factor IX by 0.8%.

Accordingly, the following formula is provided for dosage calculations:

$$\text{Number of Factor IX IU required} = \text{bodyweight (kg)} \times \text{desired Factor IX increase (\% of normal)} \times 1.2$$

It must, however, be emphasized that the response to treatment will vary from patient to patient. Larger doses than those derived from the above formula may be required; particularly if treatment is delayed. Exact dosage determination should be based on localization and extent of hemorrhage, and the level of Factor IX to be achieved. It must be emphasized that particularly with severe hemorrhage and major surgery, close laboratory monitoring of the Factor IX level is required to determine proper dosage.

Management of Specific Types of Bleeding⁵⁻⁸

Approximate Factor IX levels, typical initial doses, and the average duration of treatment are suggested in the table below. For minor bleeding a single dose will usually be sufficient, otherwise a second dose may be given after 24 hours. More severe hemorrhage will require the administration of several doses at approximately 24 hours intervals. For maintenance therapy, usually two thirds of the initial dose is infused.

Type of Bleeding	Approximate Factor IX Level (% Normal)	Typical Initial Dose (IU/kg)	Average Duration of Treatment (Days)
Minor Early hemarthrosis, minor epistaxis, and gingival bleeding, mild hematuria	20	25-35	1
Moderate Severe joint bleeding, early hematoma, major open bleeding, minor trauma, minor hemoptysis, hematemesis, and melena, major hematuria	40	40-55	2 or until adequate wound healing
Major Severe hematoma, major trauma, severe hemoptysis, hematemesis, and melena	≥ 60*	60-70	2-3 or until adequate wound healing

*For patients predisposing to thrombosis see "PRECAUTIONS" section.

Management of Surgical Procedures⁵⁻⁸

Dosage guidelines for surgical procedures are suggested below. The preoperative loading dose should be administered one hour prior to surgery. Depending on the type of surgery, replacement therapy has to be continued over one to several weeks until adequate wound healing is achieved. The average treatment interval will initially be 12 hours, while in the later postoperative period 24 hours is adequate.

Type of Surgery	Day of Operation		Init. Postop. Period (1st to 2nd Week)		Late Postop. Period (from 3rd Week Onwards)	
	Approx. Level F IX (% Normal)	Dose (IU/kg)	Approx. Level F IX (% Normal)	Dose (IU/kg)	Approx. Level F IX (% Normal)	Dose (IU/kg)
Major	≥ 60*	70-95	60-20	70-35	20	35-25
Minor	40-60	50-60	40-20	55-25	N/A	N/A

*For patients predisposing to thrombosis see "PRECAUTIONS" section. N/A: Not Applicable.

For tooth extraction the same initial dose as for minor surgery is recommended.

One infusion should be sufficient. In case of extraction of several teeth, replacement therapy for up to one week may be necessary using the same doses as for minor surgery.^{4,6}

Reconstitution

BEBULIN should be administered within 3 hours after reconstitution. The solution does not contain a preservative.

For reconstitution proceed as follows:

1. Warm both diluent and concentrate in unopened vials to room temperature (not above 37 °C, 98 °F).
2. Remove caps from both vials to expose central portions of the rubber stoppers.

3. Cleanse exposed surface of the rubber stoppers with germicidal solution and allow to dry.
4. Using aseptic technique, remove protective covering from one end of the double-ended needle and insert the exposed end through the diluent vial stopper.
5. Remove protective covering from the other end of the double-ended needle. Do not touch the exposed end. Invert diluent vial over the concentrate vial, then insert free end of the needle through the concentrate vial stopper. Diluent will be drawn into the concentrate vial by vacuum.
6. Disconnect the two vials by removing needle from the concentrate vial stopper. Gently agitate or rotate the concentrate vial until all material is dissolved.

Do not refrigerate after reconstitution!

Administration

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.

Intravenous Injection

1. After reconstituting the concentrate as described above, attach the enclosed filter needle to a sterile disposable syringe using aseptic technique. Insert filter needle through the concentrate vial stopper.
2. Inject air and withdraw solution into the syringe.
3. Remove and discard filter needle. Attach a suitable intravenous needle or infusion set with winged adapter.
4. Administer the solution intravenously at a rate comfortable to the patient (maximum rate 2 mL per minute).

HOW SUPPLIED

BEBULIN is supplied in single dose vials (NDC 64193-445-02) with Sterile Water for Injection, U.S.P., double-ended needle, and filter needle for reconstitution and withdrawal.

The vial stopper of the 20 mL Sterile Water for Injection may contain Dry Natural Rubber Latex.

Factor IX activity in International Units is stated on the label of each vial.

STORAGE

When stored at refrigerated temperature (2°C-8°C, 35°F-46°F), BEBULIN is stable for the period indicated by the expiration date on its label. Avoid freezing, which may damage the diluent vial.

REFERENCES

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