BEBULIN

(Factor IX Complex),

Nanofiltered and Vapor Heated

Lyophilized Powder for Reconstitution for Intravenous Administration

DESCRIPTION

BEBULIN (Factor IX Complex), Nanofiltered and Vapor Heated is a purified, sterile, 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), 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. Validated 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, DEAE-Sephadex adsorption contributes to the virus safety profile of BEBULIN. Despite these measures, this product can still potentially transmit disease³ (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 log$_{10}$ Reduction Factors (RFs) For Each Virus and Manufacturing Step*

<table>
<thead>
<tr>
<th>Virus Type</th>
<th>Enveloped RNA</th>
<th>Enveloped DNA</th>
<th>Non-enveloped RNA</th>
<th>Non-enveloped DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus Family</td>
<td>Retroviridae</td>
<td>Flaviviridae</td>
<td>Herpesviridae</td>
<td>Picornaviridae</td>
</tr>
<tr>
<td>HIV-1</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>1.4</td>
</tr>
<tr>
<td>BVDV</td>
<td>35 nm</td>
<td>&gt; 6.4</td>
<td>&gt; 2.0</td>
<td>&gt; 6.0</td>
</tr>
<tr>
<td>PRV</td>
<td>&gt; 7.1</td>
<td>&gt; 7.4</td>
<td>&gt; 4.5</td>
<td>≤ 1.0</td>
</tr>
<tr>
<td>HAV</td>
<td>&gt; 13.2</td>
<td>&gt; 9.1</td>
<td>&gt; 13.4</td>
<td>&gt; 7.6</td>
</tr>
<tr>
<td>MMV</td>
<td>Nanofiltration†</td>
<td>V-Vapor-Heat Treatment</td>
<td>Overall log reduction factor (ORF)</td>
<td></td>
</tr>
<tr>
<td>n.d.: Not done</td>
<td>&gt; 9.1</td>
<td>&gt; 1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

**Studies on B19V, which are considered experimental in nature, have demonstrated a virus reduction factor of not more than 3.6 log$_{10}$ and 4.6 log$_{10}$ by DEAE-Sephadex adsorption and vapor –heat treatment, respectively.

†Studies on West Nile Virus (WNV), have demonstrated a virus reduction factor of 3.1 log$_{10}$ by the 35 nm nanofiltration step.
CLINICAL PHARMACOLOGY

BEBULIN is a combination of vitamin K-dependent clotting factors (Factor IX, II, X) and 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 using the former International Standard, WHO 72/32 and was found to be 53.3% ± 9.6%, 57.5% ± 21.8%, and 53.24% ± 16.95%, respectively. In the same studies, using different methodologies, half-lives were determined to be 19.4 hrs ± 3.8 hrs, 24.6 hrs ± 3.2 hrs, and 19.97 hrs ± 8.24 hrs, respectively.¹

INDICATIONS AND USAGE

BEBULIN is indicated for the prevention and control of bleeding episodes in adult patients with hemophilia B (congenital Factor IX deficiency or Christmas disease). 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

BEBULIN is contraindicated in patients with

- Known history of hypersensitivity reactions to the product
- Known allergy to heparin
- Known history of heparin-induced thrombocytopenia

WARNINGS

**Thrombosis**

Thromboembolic events (deep vein thrombosis, pulmonary embolism, thrombotic stroke) as well as disseminated intravascular coagulation (DIC) have been reported with BEBULIN. The risk of thromboembolic complications including DIC and hyperfibrinolysis is higher in patients with congenital or acquired coagulation disorders, with repeated dosing or high doses of BEBULIN. Because of the risk of thromboembolic complications, closely monitor patients when administering BEBULIN:

- Monitor patients closely for signs and symptoms of intravascular coagulation or thrombosis.
- Monitor Factor IX level in patients predisposed to thromboembolic complications including patients with a history of coronary artery disease, patients with liver disease, pre- or postoperative patients, and neonates.
- Stop the infusion immediately and initiate appropriate diagnostic and therapeutic measures at the first signs or symptoms of thrombosis or embolism.

Anaphylaxis and Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions have been reported with BEBULIN. Manifestations of hypersensitivity or allergic reactions include anaphylactic shock, hypotension, hypertension, chest tightness, dizziness, paresthesia, lethargy, restlessness, vomiting, urticaria, erythema, pyrexia, chills, and rash. In the event of an anaphylactic/anaphylactoid reaction, stop the infusion immediately and administer appropriate emergency treatment. Evaluate patients experiencing allergic reactions for the presence of an inhibitor.

Development of Inhibitor

Formation of circulating antibodies inhibiting Factor IX has been reported with the administration of BEBULIN. If such an inhibitor occurs, the condition will manifest itself as a poor clinical response. Nephrotic syndrome has been reported following attempted immune tolerance induction in hemophilia B with Factor IX inhibitor receiving factor IX products including BEBULIN. The safety and efficacy of using factor IX products including Bebulin for immune tolerance induction have not been established.

Transmission of Infectious Agents

Because BEBULIN is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the classic Creutzfeldt-Jakob disease agent. This also applies to unknown or emerging viruses and other pathogens. No cases of transmission of viral diseases or vCJD have been associated with BEBULIN.

ALL infections thought by a physician to possibly have been transmitted by this product should be reported by the physician or other healthcare provider to Baxalta US Inc., at 1-800-423-2090 (in the U.S.).
PRECAUTIONS

Interference with Heparin Sensitivity Laboratory Testing

BEBULIN contains heparin. Take heparin content into account when performing clotting tests sensitive to heparin.

Information for Patients

Inform patients of all 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 and seek emergency care immediately for serious symptoms.

Inform patients of all signs and symptoms of parvovirus B19 infection, which is especially serious in 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.

Drug Interactions

No drug interaction studies were performed. The effect of vitamin K antagonists (e.g. warfarin) can be temporarily overcome by the administration of human prothrombin complex products, including BEBULIN, which provides increased plasma levels of functional vitamin-K dependent coagulation Factors (II, IX and X)\(^6\).

Pregnancy

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.

Pediatric Use

The safety and efficacy of the use of BEBULIN in pediatric patients have not been established.

ADVERSE REACTIONS

Clinical Trial Experience

*Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.*

The following adverse reactions were reported in clinical studies with a previous formulation of BEBULIN:

Hypotension, Dizziness, Urticaria, Erythema, Pyrexia, and Chills.
The formation of inhibitor antibodies to Factor IX has been observed with the administration of BEBULIN.

**Postmarketing Experience**

*Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.*

Table 2 lists the adverse reactions reported during postmarketing use of BEBULIN.

<table>
<thead>
<tr>
<th>Blood and Lymphatic System Disorders</th>
<th>Disseminated intravascular coagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune System Disorders</td>
<td>Anaphylactic/Anaphylactoid reactions, Hypersensitivity</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Headache</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Thromboembolic events (including Deep vein thrombosis, Pulmonary embolism, Thrombotic stroke), Flushing</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td>Dyspnea, Bronchospasm, Wheezing, Cough</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Abdominal pain, Nausea</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Angioedema, Facial edema, Rash, Pruritus</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Nephrotic syndrome (following attempted immune tolerance induction)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Infusion site reactions, including Infusion site pain</td>
</tr>
</tbody>
</table>

In addition to reactions listed above, myocardial infarction has been identified in the published literature with other Factor IX products.

**DOSAGE AND ADMINISTRATION**

**For intravenous administration only**

One International Unit (IU) 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:

\[
\text{Number of Factor IX IU required} = \text{bodyweight (kg)} \times \text{desired Factor IX increase} \times 1.2.
\]
The response to treatment will vary from patient to patient. Exact dosage determination should be based on localization and extent of hemorrhage, and the level of Factor IX to be achieved. Close laboratory monitoring of the Factor IX level is required to determine proper dosage, particularly with severe hemorrhage and major surgery. Larger doses than those derived from the above formula may be required; particularly if treatment is delayed.

Management of Bleeding\textsuperscript{7-11}.

Approximate desired Factor IX levels, typical initial doses, and the average duration of treatment are suggested in Table 3. 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 several doses at approximately 24-hours intervals. For maintenance therapy, usually two thirds of the initial dose is infused.

Table 3.
Management of Specific Types of Bleeding

<table>
<thead>
<tr>
<th>Type of Bleeding</th>
<th>Approximate Desired Factor IX Level (% Normal)</th>
<th>Typical Initial Dose (International Units/kg)</th>
<th>Average Duration of Treatment (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>20</td>
<td>25-35</td>
<td>1</td>
</tr>
<tr>
<td>Early hemarthrosis, minor epistaxis, and gingival bleeding, mild hematuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>40</td>
<td>50-65</td>
<td>2 or until adequate wound healing</td>
</tr>
<tr>
<td>Severe joint bleeding, early hematoma, major open bleeding, minor trauma, minor hemoptysis hematemesis, and melena, major hematuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>≥60*</td>
<td>75-90</td>
<td>2-3 or until adequate wound healing</td>
</tr>
<tr>
<td>Severe hematoma major trauma, Severe hemoptysis, hematemesis, and melena</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For patients predisposing to thrombosis see Precautions section.
Management of Surgical Procedures

Dosage guidelines for surgical procedures are suggested in Table 4. Administer preoperative loading dose one hour prior to surgery. Depending on the type of surgery, continue replacement therapy 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.

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Day of Operation</th>
<th>Init. Postop. Period (1st to 2nd Week)</th>
<th>Late Postop. Period (from 3rd Week Onwards)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Approx. Level Factor IX (% Normal)</td>
<td>Dose (IU/kg)</td>
<td>Approx. Level Factor IX (% Normal)</td>
</tr>
<tr>
<td>Minor</td>
<td>40 - 60</td>
<td>50 - 75</td>
<td>20 - 40</td>
</tr>
<tr>
<td>Major</td>
<td>≥60*</td>
<td>75 - 90</td>
<td>20 - 60</td>
</tr>
</tbody>
</table>

*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 and 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.

Reconstitution

- Do not mix BEBULIN with other medicinal products or solvents, other than the enclosed sterilized water for injection.
- Administer BEBULIN within 3 hours after reconstitution as the solution does not contain a preservative. **Do not refrigerate after reconstitution.**

1. Warm unopened vials of both diluent and concentrate to room temperature (not to exceed 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.

Administration

For Intravenous Administration Only.

- Parenteral drug products should be inspected for particulate matter and discoloration prior to administration.
- The reconstituted product should be colorless to slightly yellowish and clear to slightly turbid solution. Do not administer if particulate matter or discoloration is found and notify Baxalta immediately.
- Record the name of the patient and batch number of the product in order to maintain a link between the patient and the batch of the product.

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. The infusion rate should not exceed 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. Factor IX activity in international units is stated on the label of each vial.

STORAGE

Store at refrigerated temperature (2°C-8°C, 35°F-46°F). Do not use BEBULIN past the expiration date printed on the unit carton. Do not freeze.
REFERENCES

To enroll in the confidential, Industry-wide Patient Notification System, call 1 888-873-2838.

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