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Baxter

Bebulin® VH, Factor IX Complex, Vapor Heated

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DESCRIPTION

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

Bebulin VH, Factor IX Complex, Vapor Heated is standardized in terms of Factor IX content and each vial is labeled for the Factor IX content indicated in International Units (I.U.). One International Unit of Factor IX (according to the current International Standard for Human Blood Coagulation Factors II, IX, and X in Concentrates, Code 84/681) corresponds to the activity of Factor IX in 1 mL of fresh normal human plasma.

CLINICAL PHARMACOLOGY

Bebulin VH, Factor IX Complex, Vapor Heated is a combination of vitamin K-dependent clotting factors found in normal plasma. The administration of Bebulin VH, Factor IX Complex, Vapor Heated 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 VH, Factor IX Complex, Vapor Heated was determined by investigators in Germany, Japan, and the United States using the former International Standard, WHO 72/32 and 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, 2, 3).

The product has been subjected to virus inactivation by vapor heating where vapor is first applied for 10 hours at 60°C ±0.5°C and an excess pressure of 190 ±25 mbar followed by 1 hour at 80°C ±0.5°C and an excess pressure of 375 ±35 mbar (4). The effectiveness of vapor heating was evaluated in vitro using Human Immunodeficiency Virus (HIV-1) and Sindbis Virus. Lyophilization followed by vapor heat treatment at 60°C inactivated >5.8 logs of HIV-1 and 4.0 logs of Sindbis Virus within 3 hours. Lyophilization with vapor heating at 60°C for 10 hours resulted in no detectable Sindbis Virus (>4.5 log reduction). Vapor heating at 80°C inactivated >3.5 logs of HIV-1 and >4.4 logs of Sindbis Virus within one hour.

In the context of two prospective clinical studies (5, 6) and a retrospective survey (7) Bebulin VH, Factor IX Complex, Vapor Heated 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 could be followed up for nonA, nonB hepatitis, 9 for HCV seroconversion, 3 for hepatitis B, and 24 for HIV seroconversion. None tested positive for any of these infections. An additional 3 patients with 2 or more consecutive test samples missing tested negative for nonA, nonB hepatitis for all samples available. Three studies using ICTH criteria for testing (5, 6, 8), a retrospective survey (7), and a case report (9) on other vapor heated factors of the prothrombin complex that were subjected to the same inactivation process as BEBULIN VH gave the following results: 27 patients tested negative for nonA, nonB hepatitis, 15 for HCV seroconversion, 25 for hepatitis B, and 75 for HIV seroconversion.

INDICATIONS AND USAGE

Bebulin VH, Factor IX Complex, Vapor Heated is indicated for the prevention and control of hemorrhagic episodes in hemophilia B patients.

Bebulin VH, Factor IX Complex, Vapor Heated 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

Bebulin VH, Factor IX Complex, Vapor Heated 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 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.). 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 nonA, nonB hepatitis. Hepatitis B vaccination is essential for patients with hemophilia and it is recommended that this be done at birth or diagnosis.

The risk of thromboembolic complications including 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.

PRECAUTIONS

In patients with risk factors predisposing to thrombosis the Factor IX level should not be raised to more than approximately 60% of normal (10). In addition, it is recommended that such patients as well as patients who require high doses of Factor IX because of major surgical interventions be monitored for the possible development of DIC and/or thrombosis. In case changes occur in blood pressure or pulse rate or symptoms such as respiratory distress, chest pain or cough, treatment should be stopped immediately.

Information for Patients

Some viruses, such as parvovirus B19 or hepatitis A, 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. Evidence of hepatitis A may include several days to weeks of poor appetite, tiredness, and low-grade fever followed by nausea, vomiting, and pain in the belly. Dark urine and a yellowed complexion are also common symptoms. Patients should be encouraged to consult their physician if such symptoms appear.

Patients should be informed of the early signs of hypersensitivity reactions such as fever, urticaria, rashes, nausea or retching and should be advised to discontinue use of the product and contact their physician if these symptoms occur.

Pregnancy Category C.

Animal reproduction studies have not been conducted with Bebulin VH, Factor IX Complex, Vapor Heated. It is also not known whether Bebulin VH, Factor IX Complex,Vapor Heated can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Bebulin VH, Factor IX Complex, Vapor Heated should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

As with any other infused plasma derivatives, anaphylactoid or anaphylactic reactions may occur in rare cases. The occurrence of these reactions (e.g. fever, urticarial rashes, nausea, retching, dyspnea, anaphylactic shock) necessitates the interruption of replacement therapy. Mild reactions can be managed with antihistamines; severe hypotensive reactions require immediate intervention using current principles of shock therapy.

DOSAGE AND ADMINISTRATION

General

Bebulin VH, Factor IX Complex, Vapor Heated is intended 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:

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

It must, however, be emphasized that the response to treatment will vary from patient to patient and that occasionally larger doses than those derived from the above formula will 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.

Type of Bleeding	Approximate Factor IX Level (% Normal)	Typical Initial Dose (I.U./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.

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 Bleeding (10, 11, 12, 13, 14)

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 hour intervals. For maintenance therapy usually two thirds of the initial dose is infused.

Management of Surgical Procedures (10, 11, 12, 13, 14)

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 are generally 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 (I.U./kg)	Approx. Level F IX (% Normal)	Dose (I.U./kg)	Approx Level F IX (% Normal)	. Dose (I.U./kg)
Major	≥60*	70–95	60→20	70→35	20	35→25
Minor	40–60	50–60	40→20	55→25		

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

For tooth extraction the same initial dose as for minor surgery is recommended. Generally, one infusion will 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 (12, 13, 14).

Long-Term Prophylactic Treatment

Prophylactic doses of 20 – 30 I.U./kg administered once, or preferably up to twice a week have been shown to significantly reduce the frequency of spontaneous hemorrhage (12, 15). It is, however, recommended that prophylactic dosage regimens be tailored to individual needs.

Reconstitution

Bebulin VH, Factor IX Complex, Vapor Heated should be reconstituted immediately before application. The solution does not contain a preservative and must be used within 3 hours of reconstitution.

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, taking care not to 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 VH, Factor IX Complex, Vapor Heated is supplied in single dose vials with Sterile Water for Injection, U.S.P. (This Product Contains Dry Natural Rubber.), double-ended needle, and filter needle for reconstitution and withdrawal.

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

Rx only

STORAGE

When stored at refrigerator temperature (2°C – 8°C, 35°F – 46°F),

Bebulin VH, Factor IX Complex, Vapor Heated is stable for the period indicated by the expiration date on its label.

Avoid freezing, which may damage the diluent vial.

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