Coagulation Factor IX (Human) Mononine®

Mononine® is a sterile, lyophilized concentrate of Factor IX prepared from pooled human plasma and is intended for use in therapy of Factor IX deficiency, known as Hemophilia B or Christmas disease. Mononine® is purified by an immunoaffinity chromatography process using the rabbit anti-human Factor IX immune serum. After preparation, this concentrate is further purified and sterile-filtered using a 0.22 micron filter. The immunoaffinity chromatography process utilized results in a highly pure Factor IX preparation. It shows a single prominent band of 265,000 molecular weight on SDS-polyacrylamide gel electrophoresis and has a specific activity of not less than 190 IU per mg at 25°C.

All Source Plasma used in the manufacture of this product was tested by FDA-licensed Nucleic Acid Testing (NAT) for HIV, HCV and HBV and found to be nonreactive (negative).

This concentrate is prepared by mononuclear immunoadsorption chromatography during its manufacture, which has been shown to be capable of reducing the risk of viral transmission. Additionally, a chemical treatment protocol and filtration used in its manufacture have also been shown to be capable of reducing the risk of viral transmission. The risk of viral infection from coagulation factor concentrates (see CLINICAL PHARMACOLOGY and WARNINGS).

Mononine® is a purified preparation of Factor IX. When stored as directed, it will maintain its labeled potency for the period indicated on the container label.

Each vial contains the labeled amount of Factor IX expressed in International Units (IU). One IU represents the activity of 1.0 unit of Factor IX, defined as the amount of Factor IX necessary to convert prothrombin to thrombin at 25°C, in the presence of optimal concentrations of all necessary coagulation factors in a thromboplastin solution, at a final concentration of 0.02M calcium chloride. Each ml of the reconstituted concentrate contains approximately 100 IU of Factor IX and non-detectable levels of Factors VII and VII and ≤0.025 IU per ml of APTT, using standard coagulation assays. Each vial also contains histidine (10 mM), sodium chloride (approx. 0.066 M), mannitol (approx. 3%) and polysorbate 80 (approx. 0.0075%). The pH is approximately 5.5.

Intramuscular or subcutaneous injection of this concentrate should be avoided since it is a highly viscous material. The material will remain as a liquid at room temperature. The material is a clear, pale yellow, colorless solution.

Unable to be ruled out.

The infusion of exogenous Factor IX to replace the deficiency present in Hemophilia B temporarily restores the patient to a near-normal coagulation state.

The virus safety of Mononine® has been studied in clinical trials of two cohorts of hemophilia B subjects previously exposed to blood or blood products. 5 One cohort of subjects included those with moderate to severe Factor IX deficiency requiring chronic replacement therapy (41 subjects were dosed); the second cohort included subjects with a mild deficiency requiring factor IX replacement for surgical procedures (10 subjects were dosed).

These subjects were followed for serum alamin ammonia transferase (ALT) elevations, as well as for a range of viral serologies. Thirty-seven (37) subjects (30 with moderate to severe deficiency and seven with a mild deficiency) were evaluated for evidence of virus hepatitis safety by the International Society on Thrombosis and Hemostasis-Scientific and Transfusion-Guidelines Committee criteria. None of these subjects showed evidence of transmission of hepatitis A, B, C, or HIV.

Mononine® contains trace amounts of the murine monoclonal antibody (mAb) used in its purification (≤0.5 μg per ml of factor IX). This mAb was not associated with the formation of prothrombin activation fragment (F1+2) whereas the Factor IX Complex was associated with the formation of prothrombin activation fragment (F1+2).5,7

Factor IX inhibitors are associated with the formation of prothrombin activation fragment (F1+2). During the period from 1992 to 1996, five subjects showed transient ALT elevations that were greater than twice the upper normal limit. These subjects were investigated thoroughly and none of the ALT elevations was associated with liver disease. In three of the five subjects, a single ALT elevation greater than 7 times the upper limit of normal was recorded during the course of the study. No concomitant symptoms occurred and the liver function tests did not reveal any abnormalities. In addition, in one of these three subjects with single ALT elevations, a relationship to Mononine® could be excluded due to a span of 18 months between the injection of Mononine® and occurrence of the elevated ALT level. In one of the two remaining subjects, the ALT level was elevated prior to the first infusion of Mononine® and normalized thereafter. Subsequently, this subject’s ALT levels were elevated intermittently over a period of 24 months, which appeared to be temporally related to the administration of concomitant medications: atorvastatin, amoxicillin, amoxicillin, chloramphenicol and halothane. These medications are known to cause liver enzyme elevations. Furthermore, in both studies, there were no clinical signs of liver disease. Therefore, in the absence of evidence of liver disease, the remaining factor of the five was found to have recurring ALT elevations that persisted for a period of five months, gradually decreasing to normal levels. Approximately three days after his first infusion this subject developed nausea, vomiting, anorexia and hypotension. His first episode of hepatitis B. At that time, the subject’s ALT level was slightly above the upper limit of normal (55 IU/L, upper limit of normal 35). Five days later, the subject experienced flu-like symptoms with fever, nausea and vomiting. The subject was treated with amoxicillin and promethazine. The ALT value recorded eight days thereafter (approximately 13 days after the Mononine® infusion) was found to be clearly elevated at 629 IU/L. ALT levels subsequently decreased again and returned to the normal range of 100 to 220 IU/L. The origin of these infections was unknown as no other clinical or laboratory evidence of hepatitis A, B, C or D was available. In addition to the ALT elevations, there was no evidence of hepatitis A, B, C or D. This subject’s idiosyncratic spikes in liver enzymes and gastrointestinal symptoms were considered to be of viral origin. However, a causal relationship between prior administration of Mononine® and these aminotransferase elevations and mild symptoms could not be ruled out.

Mononine® is indicated for the prevention and treatment of bleeding in Factor IX deficiency, also known as Hemophilia B or Christmas disease.

Limitation of Use

Mononine® is not indicated in the treatment or prophylaxis of Hemophilia A patients with inhibitors to Factor VIII.

Mononine® contains non-detectable levels of Factors VIII and IX and x0.0025 IU per ml Factor IX unit using standard coagulation assays) and, therefore, not indicated for replacement therapy of these clotting factors. Mononine® is also not indicated in the treatment or reversal of coumarin-induced anticoagulation or in a hemostatic state caused by hepatitis-induced lack of production of liver dependent coagulation factor.

The use of blood or blood products in patients with Factor IX inhibitors and a history of severe allergic reactions to bovine or porcine components may still potentially contain human pathogenic agents, including those not yet known or identified. Thus the risk of transmission of infectious agents cannot be totally eliminated. Any infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other health-care provider to CSL Behring at 1-866-915-6958 (in the U.S. and Canada). 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 noroviruses, rotavirus, hepatitis, (See Information For Patients.)

Cardiovascular Complications

Since the use of Factor IX Complex concentrates has historically been associated with the development of thrombotic complications, the use of Mononine® containing-contents should be extremely cautious in patients with signs of fibrinoid and in patients with disseminated intravascular coagulation (DIC). In patients with existing cardiovascular risk factors, substitution therapy with FIX may increase the cardiovascular risk.

Hypersensitivity Reactions

Hypersensitivity and allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all Factor IX concentrates. Frequently, these reactions occur in patients with a history of previously involving injections of Factor IX inhibitors. Patients should be informed of the early symptoms and signs of hypersensitivity reactions, including hives, generalized urticaria, angioedema, asthma, pruritus, hypotension, tachycardia, and angina. Patients should be advised to discontinue use of product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if any allergic reactions occur.

Neutralizing Antibodies

Preliminary information suggests a relationship may exist between the presence of major deletion mutations in the factor IX gene and an increased risk of inhibitor formation and of acute hypersensitivity reactions. Patients known to have major deletion mutations of the factor IX gene should be observed closely for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of initial exposure to product.

Nephrotic Syndrome

Nephrotic syndrome has been reported following attempted immune tolerance induction with factor IX product. Five hemophilia B patients with factor IX inhibitors were treated with factor IX. The safety and efficacy of using Mononine® in attempted immune tolerance induction has not been established.

PRECAUTIONS

Thrombocytopenia

Extensive clinical experience suggests that there is a lower risk of thromboembolic complications with the use of Mononine®.
use of Mononine® than with prothrombin complex concentrates. However, as with all products containing Factor IX, consider the risk of thrombomodulin when administering Mononine® to patients with liver disease, as a reduced clearance may take place that is related to the administration of Mononine®, the rate of infusion would be decreased or the infusion stopped, as dictated by the response of the patient. The infusion should be stopped promptly and appropriate countermeasures and supportive ther-

apy should be administered to prevent an acute hypersensitivity reaction or a reaction that results in anaphylaxis.

During the course of treatment, determination of daily Factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to Mononine®, achieving different levels of in vivo recovery and demonstrating different half-lives.

Cardiovascular Disease

The use of high doses of Factor IX Complex concentrates has been reported to be associated with instances of mononuclear cell disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. A Factor IX level of 25-50% [IU/dL] is considered adequate for hemostasis, including major hemorrhages and surgery. Attempting to maintain Factor IX levels of 75-100% [IU/dL] during treat-

ment is not routinely recommended nor required. To achieve Factor IX levels that will remain above 25% [IU/dL] between once a day administration, each daily dose should attempt to raise the 30-minute post-

infusion Factor IX level to 50-60% [IU/dL] (see DOSAGE AND ADMINISTRATION).

No controlled studies have been available regarding the use of E. coli amino caproic acid or other antifibrinolytic agents following an initial infusion of Mononine® for the prevention or treatment of oral bleeding following trauma or dental procedures such as extractions.

Information for Patients

Patients should be informed of the early symptoms and signs of hypersens-

itivity reactions including hives, generalized urticaria, tightness of the chest, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Patients should be advised to discontinue the use of the product and consult their physician and/or seek immediate emergency care, depending on the severity of the reaction, if any of these symptoms occur.

Women such as those taking oral contraceptives are at increased risk. In general, patients should be informed of the possible risk of thrombosis in pregnancy or for any woman who may become pregnant. In general, all patients should be informed of the risk of death associated with embolism.

Cautions

The following adverse reactions have been spontaneously reported during post-marketing use of Mononine® as well as with other plasma-derived Factor IX concentrates: headache, fever, chills, flushing, nausea, vomiting, chest or back pain, dyspnea, hypotension, anaphylactic, urticaria, angioedema, pruritus, and anaphylactic shock reactions. In a clinical study with Mononine® in previously untreated hemophilia B patients, five patients experienced ALT elevations. Serologic tests for hepatitis A, hepatitis B, hepatitis C, Cytomegalovirus, and Epstein-Barr virus were negative.

Postmarketing Experience

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

Administration

Intravenous Injection

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Storage

At stored temperature at 2-8 °C (36-46 °F), Mononine® is stable for the period indicated by the expiration date on its label. Within this period, Mononine® may be stored at room temperature not to exceed 25°C (77°F), for up to one month.

Avoid freezing, which may damage container for the diluent.

HOW SUPPLIED

Mononine® is supplied in a single dose vial with Sterile Water for Injection, USP, double-ended needle for reconstitution.

In the presence of an inhibitor to Factor IX, higher doses of Mononine® might be necessary to overcome the inhibitor (see PRECAUTIONS). No data on the treatment of patients with inhibitors to Factor IX with Mononine® are available.

For information on rate of administration, see Rate of Administration, below.

Reconstitution

1. Using aseptic technique, attach the vented filter spike to a sterile disposable syringe.

2. Insert the vented filter spike into the stopper of the Mononine® vial, invert the vial, and position the filter spike so that the orifice is at the inside edge of the stopper.

3. Withdraw the reconstituted concentrate into the syringe.

4. Discard the filter spike. Perform aseptic technique to avoid introducing any air into the concentrate. Attach the syringe to the luer end of the tubing.

5. The rate of infusion should be decreased or stopped, as dictated by the response of the patient.

6. The amount of Mononine® to be infused, as well as the frequency of infusions, will vary with each patient and with the clinical situation.

7. As a general rule, the level of Factor IX required for treatment of different conditions is as follows:

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Reconstitution

1. Compress both the diluent and Mononine® in unopened vials to room temperature not above 37°C (99°F).

2. Remove the caps from both vials to expose the central portions of the rubber stoppers.

3. Treat both surfaces of the rubber stoppers with alcohol solution and allow them to dry.

4. Using aseptic technique, insert one end of the double-ended needle into the rubber stopper of the dilu-

ent vial. Insert the diluent vial and inset the other end of the double-ended needle into the rubber stopper of the Mononine® vial.

5. One reconstituted vial of Mononine® (1000 IU) is equivalent to 1 IU/kg, i.e., to approximately 0.100 IU/kg, Mononine® should be administered at a rate of approximately 2.0 mL per minute.

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