

**PRESCRIBING INFORMATION**  
**COAGULATION FACTOR IX (HUMAN)**

**MONONINE®**  
**MONOCLONAL ANTIBODY PURIFIED**

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U.S. License No. 1281



Aventis Behring

**R only**  
**DESCRIPTION**

Coagulation Factor IX (Human), Mononine®, is a sterile, stable, 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. Coagulation Factor IX (Human), Mononine®, is purified of extraneous plasma-derived proteins, including Factors II, VII and X, by use of immunoaffinity chromatography. A murine monoclonal antibody to Factor IX is used as an affinity ligand to isolate Factor IX from the source material. Factor IX is then dissociated from the monoclonal antibody, recovered, purified further, formulated and provided as a sterile, lyophilized powder. The immunoaffinity protocol utilized results in a highly pure Factor IX preparation. It shows predominantly a single component by SDS polyacrylamide electrophoretic evaluation and has a specific activity of not less than 190 Factor IX units per mg total protein.

The plasma used in the manufacture of this product has been tested and found negative for HBV, HCV, and HIV-1 by an investigational test procedure referred to as Nucleic Acid Testing (NAT) using Polymerase Chain Reaction (PCR) Technology. Investigational testing is being performed to determine the effectiveness of NAT to detect low levels of viral material. The significance of a negative result is unknown since the effectiveness of the test has not been established.

This concentrate has been processed by monoclonal antibody immunoaffinity chromatography during its manufacture which has been shown to be capable of reducing the risk of viral transmission. Additionally, a chemical treatment protocol and two sequential ultrafiltration steps used in its manufacture have also been shown to be capable of significant viral reductions. However, no procedure has been shown to be totally effective in removing the risk of viral infectivity from coagulation factor concentrates (see **CLINICAL PHARMACOLOGY** and **WARNINGS**).

Mononine® is a highly 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 activity expressed in International Units (IU). One IU represents the activity of Factor IX present in 1 mL of normal, pooled plasma. When reconstituted as recommended, the resulting solution is a clear, colorless, isotonic preparation of neutral pH, containing approximately 100 times the Factor IX potency found in an equal volume of plasma. Each mL of the reconstituted concentrate contains approximately 100 IU of Factor IX and non-detectable levels of Factors II, VII and X (<0.0025 IU per Factor IX unit using standard coagulation assays). It also contains histidine (approx. 10mM), sodium chloride (approx. 0.066M) and mannitol (approx. 3%). Hydrochloric acid and/or sodium hydroxide may have been used to adjust pH. Mononine® also contains trace amounts (≤ 50 ng mouse protein/100 Factor IX activity units) of the murine monoclonal antibody used in its purification (see **CLINICAL PHARMACOLOGY**).

Mononine® is to be administered only intravenously.

**CLINICAL PHARMACOLOGY**

Hemophilia B, or Christmas disease, is an X-linked recessively inherited disorder of blood coagulation characterized by insufficient or abnormal synthesis of the clotting protein Factor IX. Factor IX is a vitamin K-dependent coagulation factor, which is synthesized in the liver. Factor IX is activated by Factor XIa in the intrinsic coagulation pathway. Activated Factor IX (IXa), in combination with Factor VIIIc, activates Factor X to Xa, resulting ultimately in the conversion of prothrombin to thrombin and the formation of a fibrin clot. The infusion of exogenous Factor IX to replace the deficiency present in hemophilia B temporarily restores hemostasis. Depending upon the patient's level of biologically active Factor IX, clinical symptoms range from moderate skin bruising or excessive hemorrhage after trauma or surgery to spontaneous hemorrhage into joints, muscles or internal organs including the brain. Severe or recurring hemorrhages can produce death, organ dysfunction or orthopedic deformity.

Infusion of Factor IX Complex concentrates that contain varying but significant amounts of the other liver-dependent blood coagulation proteins, Factors II, VII and X, into patients with hemophilia B results in Factor IX recoveries ranging from approximately 0.57-1.1 IU/dL rise per IU/kg body weight infused with plasma half-lives for Factor IX ranging from approximately 23 hours to 31 hours.<sup>1,2</sup> Infusion of Coagulation Factor IX (Human), Mononine®, into ten patients with severe or moderate hemophilia B has shown a mean recovery of 0.67 IU/dL rise per IU/kg body weight infused and a mean half-life of 22.6 hours.<sup>3</sup> After six months of experience with repeated infusions performed on the nine patients who remained in the study, it was shown that the half-life and recovery was maintained at a level comparable to that found with the initial infusion. The six-month data showed a mean recovery of 0.68 IU/dL rise per IU/kg body weight infused and a mean half-life of 25.3 hours.<sup>3</sup> The data show no statistically significant differences between the initial and six-month values.

Two studies were conducted to provide Mononine® for compassionate treatment of hemophilia B patients who required extensive Factor IX replacement for surgery, trauma, or spontaneous bleeding (73 unique patients and eight patients enrolled twice for a total of 81 patients), as well as to evaluate the safety and efficacy of Mononine®. The overall mean recovery during treatment was determined to be 1.23 ± 0.42 IU/dL rise/IU/kg (K) (range = 0.59 to 2.92 K) among the 55 patients included in recovery analyses in the one study and to be 1.12 ± 0.52 K (range = 0.61 to 2.08 K) among 10 patients included in these analyses in the second study. Five (5/81, 6%) patients reported adverse events attributed to Mononine® across the two studies. In these studies, 100 doses of Mononine® were administered at what are considered high doses for a Factor IX concentrate, a range of 71 to 161 IU/kg to a total of 36 patients. Sixty-seven (67) of these infusions were the subject of recovery analyses. Mean recovery tended to decrease as the dose of Mononine® increased: 1.09 ± 0.52 K at doses > 75-95 IU/kg (n=38), 0.98 ± 0.45 K at doses >95-115 IU/kg (n = 21), 0.70 ± 0.38 K at doses >115-135 IU/kg (n = 2), 0.67 K at doses >135-155 IU/kg (n = 1), and 0.73 ± 0.34 K at doses >155 IU/kg (n = 5). Among the 36 patients who received these high doses, only one (2.8%) reported an adverse experience with a possible relationship to Mononine® ("difficulty in concentrating"; patient recovered). In no patients were thrombotic complications observed or reported.<sup>4</sup>

The manufacturing procedure for Coagulation Factor IX (Human), Mononine®, includes multiple processing steps that have been designed to reduce the risk of viral transmission. Validation studies of the monoclonal antibody (MAB) immunoaffinity chromatography/chemical treatment steps and two sequential ultrafiltration steps used in the production of Mononine® document the viral reduction capacity of the processes employed. These studies were conducted using the Human Immunodeficiency Virus (HIV) and four model viruses representing a broad range of viral characteristics, i.e., Sindbis, Vaccinia, Vesicular Stomatitis (VSV) and Murine Encephalomyocarditis (EMC), a non-lipid encapsulated model virus. The results of these validation studies (see Table 1 below) document cumulative viral reduction capacities of ≥11.56 log<sub>10</sub> for HIV, 10.24 log<sub>10</sub> for Sindbis, 11.64 log<sub>10</sub> for EMC, ≥14.23 log<sub>10</sub> for VSV, and ≥10.90 log<sub>10</sub> for Vaccinia.

**Viral Reduction Studies Table 1**  
**(Log<sub>10</sub> Reduction)**

Processing Step	HIV	Sindbis	EMC	VSV	Vaccinia
MAB Chromatography	-	2.76	3.89	≥7.18**	≥3.60
Sodium Thiocyanate Chemical Treatment	≥4.16	0	0	**	0
Ultrafiltration***	≥7.4	7.48	7.75	7.05	≥7.30
Total Log <sub>10</sub> Reduction	≥11.56	10.24	11.64	≥14.23	≥10.90

\*MAB Chromatography not studied.

\*\*Results are for combined MAB chromatography/sodium thiocyanate step.

\*\*\*For VSV and Vaccinia these data are results for a single ultrafiltration; the data for HIV, Sindbis, and EMC are results for double ultrafiltration.

Similar viral reduction studies were conducted using porcine parvovirus (used as a model for human parvovirus B19). The results for these validation studies (see Table 2 below) document cumulative viral reduction capacity of ≥11.64 log<sub>10</sub> for porcine parvovirus.

**Viral Reduction Studies Table 2**  
**(Log<sub>10</sub> Reduction)**

Processing Step	Porcine Parvovirus
Combined MAB Chromatography and Sodium Thiocyanate Chemical Treatment	>4.28
AH Sepharose Chromatography	2.26
Ultrafiltration	5.10
Total Log <sub>10</sub> Reduction	≥11.64

**CLINICAL STUDIES**

The viral safety of Coagulation Factor IX (Human), Mononine®, has been studied in clinical trials of two cohorts of hemophilia B patients previously unexposed to blood or blood products.<sup>5</sup> One cohort of patients included those with moderate to severe factor IX deficiency requiring chronic replacement therapy (36 patients dosed thus far); the second cohort included patients with a mild deficiency requiring factor IX replacement for surgical procedures (nine patients dosed thus far).

These patients were followed for serum ALT elevations, as well as for a range of viral serologies. Thirty-two (32) patients (25 with a moderate to severe deficiency and seven with a mild deficiency) were evaluable for assessment of viral hepatitis safety by ISTH-SSC criteria. None of these patients showed evidence of transmission of hepatitis B, hepatitis C, or HIV. In two of the evaluable patients, ALT elevations were attributed to causes other than Mononine®. In addition, one patient considered unevaluable for assessment of viral safety was found to have persistent and significant ALT elevations after infusion. This patient received hepatitis B hyperimmune immunoglobulin and his first injection of hepatitis B vaccine approximately three days after his first infusion. As a result, definitive conclusions regarding the occurrence of hepatitis B in this patient cannot be made.

Coagulation Factor IX (Human), Mononine®, contains trace amounts of the murine monoclonal antibody (MAB) used in its purification (≤50 ng mouse protein/100 IU). While the levels of mouse protein are extremely low, infusion of such proteins might theoretically induce human anti-mouse antibody (HAMA) responses. To test this possibility, human IgG, IgM, and IgE antibodies to mouse IgG were assessed by immunoradiometric assay (IRMA) in 11 hemophilia B patients who received Mononine® and were previously untreated with other blood products. HAMAs were evaluated prior to the first infusion and at 2 to 42 months after initial treatment. Human IgE antibodies to mouse IgG were below the level of detectability at all time points for all patients, and there were no statistically significant increases in either human IgG antibodies or human IgM antibodies to mouse protein. In addition, an analysis of clinical data shows that no replacement factor-related adverse events occurred that might have been considered as allergic or anaphylactoid reactions.<sup>5</sup>

In clinical studies of Coagulation Factor IX (Human), Mononine®, patients were monitored for evidence of disseminated intravascular coagulation. In six patients evaluated after infusion, fibrinogen levels and platelet counts were unchanged, and fibrin degradation products did not appear.<sup>3</sup>

In further clinical evaluations of Coagulation Factor IX (Human), Mononine®, in a crossover study with a Factor IX Complex concentrate, Mononine® was not associated with the formation of prothrombin activation fragment (F<sub>1,2</sub>) whereas the Factor IX Complex was associated with the formation of prothrombin activation fragment (F<sub>1,2</sub>).<sup>3,7</sup> Prothrombin activation fragment (F<sub>1,2</sub>) is indicative of activation of prothrombin.

**INDICATIONS AND USAGE**

Coagulation Factor IX (Human), Mononine®, is indicated for the prevention and control of bleeding in Factor IX deficiency, also known as hemophilia B or Christmas disease.

Mononine® is not indicated in the treatment or prophylaxis of hemophilia A patients with inhibitors to Factor VIII. Coagulation Factor IX (Human), Mononine®, contains non-detectable levels of Factors II, VII and X (<0.0025 IU per Factor IX unit using standard coagulation assays) and is, 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 hemorrhagic state caused by heparitis-induced lack of production of liver dependent coagulation factors.

**CONTRAINDICATIONS**

Known hypersensitivity to mouse protein is a contraindication to Coagulation Factor IX (Human), Mononine®.

**WARNINGS**

Coagulation Factor IX (Human), Mononine®, is derived from human plasma that may contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents can not be totally eliminated. Stringent procedures, designed to reduce the risk of adventitious agent transmission, have been employed in the manufacture of this product from the collection and testing of plasma, through to the application of viral elimination/reduction steps. As with any pharmaceutical, the physician should weigh the risks and benefits of administration. 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.

Since the use of Factor IX Complex concentrates has historically been associated with the development of thromboembolic complications, the use of Factor IX-containing products may be potentially hazardous in patients with signs of fibrinolysis and in patients with disseminated intravascular coagulation (DIC).

Because Mononine® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

**PRECAUTIONS**

Extensive clinical experience suggests that there is a lower risk of thromboembolic complications with the use of Mononine® than with prothrombin complex concentrates. However, as with all products containing Factor IX, caution should be exercised when administering Mononine® to patients with liver disease, to patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena or DIC.<sup>8,9</sup> In each of these situations, the potential benefit of treatment with Mononine® should be weighed against the potential risk of these complications.

Coagulation Factor IX (Human), Mononine®, should be administered intravenously at a rate that will permit observation of the patient for any immediate reaction. Rates of infusion of up to 225 IU per minute have been regularly tolerated with no adverse reactions. If any reaction takes place that is thought to be related to the administration of Mononine®, the rate of infusion should be decreased or the infusion stopped, as dictated by the response of the patient.

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.

The use of high doses of Factor IX Complex concentrates has been reported to be associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. Generally a Factor IX level of 25% to 50% is considered adequate for hemostasis, including major hemorrhages and surgery. Attempting to maintain Factor IX levels of >75% to 100% during treatment is not routinely recommended nor required. To achieve Factor IX levels that will remain above 25% between once a day administrations, each daily dose should attempt to raise the level to 50-60% (see **DOSE AND ADMINISTRATION**).

No controlled studies have been available regarding the use of ε-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 signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis, and should be advised to discontinue use of the concentrate and contact their physician if these symptoms occur.

**Pregnancy Category C** – Animal reproduction studies have not been conducted with Coagulation Factor IX (Human), Mononine®. It is also not known whether Mononine® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Mononine® should be given to a pregnant woman only if clearly needed.

**Pediatric Use**

Evaluation of the safety and effectiveness of Mononine® treatment in 51 pediatric patients between the ages of 1 day and 20 years, as a part of viral safety trials and trials for surgery, trauma or spontaneous bleeding, showed that excellent hemostasis was achieved with no thrombotic complications.<sup>10</sup> Included in the experience with patients aged birth to 20 years are two long-term viral safety studies demonstrating lack of viral transmission. Dosing in children is based on body weight and is generally based on the same guidelines as for adults (see below).

**Geriatric Use**

Clinical studies of Mononine® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. As for all patients, dosing for geriatric patients should be appropriate to their overall situation.

**ADVERSE REACTIONS**

As with the administration of any product intravenously, the following reactions may be observed following administration: headache, fever, chills, flushing, nausea, vomiting, tingling, lethargy, hives, stinging or burning at the infusion site or other manifestations of allergic reactions including anaphylaxis.

There is a potential risk of thromboembolic episodes following the administration of Mononine® (see **WARNINGS** and **PRECAUTIONS**).

The patient should be monitored closely during the infusion of Mononine® to observe for the development of any reaction. If any reaction takes place that is thought to be related to the administration of Mononine®, the rate of infusion should be decreased or the infusion stopped, as dictated by the response of the patient.

**DOSE AND ADMINISTRATION**

Coagulation Factor IX (Human), Mononine®, is intended for intravenous administration only. It should be reconstituted with the volume of Sterile Water for Injection, USP supplied with the lot, and administered within three hours of reconstitution. Do not refrigerate after reconstitution. After administration, any unused solution and the administration equipment should be discarded. As a general rule, 1 IU of Factor IX activity per kg can be expected to increase the circulating level of Factor IX by 1% of normal. The following formula provides a guide to dosage calculations:

$$\text{Number of Factor IX IU required} = \frac{\text{Body Weight (in kg)} \times \text{desired Factor IX increase (\% normal)}}{1.0 \text{ IU/kg}}$$

The amount of Coagulation Factor IX (Human), Mononine®, to be infused, as well as the frequency of infusions, will vary with each patient and with the clinical situation.<sup>11,12</sup>

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

	Minor Spontaneous Hemorrhage, Prophylaxis	Major Trauma or Surgery
Desired levels of Factor IX for Hemostasis	15-25%	25-50%
Initial loading dose to achieve desired level	up to 20-30 IU/kg	up to 75 IU/kg
Frequency of dosing	once; repeated in 24 hours if necessary	every 18-30 hours, depending on T <sub>1/2</sub> and measured Factor IX levels
Duration of treatment	once; repeated if necessary	up to ten days, depending upon nature of insult

Recovery of the loading dose varies from patient to patient. Doses administered should be titrated to the patient's response. Mononine® administered in doses of  $\geq 75$  IU/kg were well tolerated (see **CLINICAL PHARMACOLOGY**).

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. Warm both the diluent and Coagulation Factor IX (Human), Mononine®, in unopened vials to room temperature [not above 37°C (98°F)].
2. Remove the caps from both vials to expose the central portions of the rubber stoppers.
3. Treat the surface of the rubber stoppers with antiseptic solution and allow them to dry.
4. Using aseptic technique, insert one end of the double-end needle into the rubber stopper of the diluent vial. Invert the diluent vial and insert the other end of the double-end needle into the rubber stopper of the Mononine® vial. Direct the diluent, which will be drawn in by vacuum, over the entire surface of the Mononine® cake. (In order to assure transfer of all the diluent, adjust the position of the tip of the needle in the diluent vial to the inside edge of the diluent stopper.) Rotate the vial to ensure complete wetting of the cake during the transfer process.
5. Remove the diluent vial to release the vacuum, then remove the double-end needle from the Mononine® vial.
6. Gently swirl the vial until the powder is dissolved and the solution is ready for administration. The concentrate routinely and easily reconstitutes within one minute. To assure sterility, Mononine® should be administered within three hours after reconstitution.
7. Product should be filtered prior to use as described under **Administration**. Parenteral drug preparations should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

#### Administration

##### Intravenous Injection

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

Plastic disposable syringes are recommended with Coagulation Factor IX (Human), Mononine® solution. The ground glass surfaces of all-glass syringes tend to stick with solutions of this type. Please note, this concentrate is supplied with a SELF-VENTING filter spike.

1. Using aseptic technique, attach the vented filter spike to a sterile disposable syringe.  
**CAUTION:** The use of other, non-vented filter needles or spikes without the proper procedure may result in air lock and prevent the complete transfer of the concentrate.  
**CAUTION: DO NOT INJECT AIR INTO THE MONONINE® VIAL.** The self-venting feature of the vented filter spike precludes the need to inject air in order to facilitate withdrawal of the reconstituted solution. The injection of air could cause partial product loss through the vent filter.
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 solution into the syringe.
4. Discard the filter spike. Perform venipuncture using the enclosed winged needle with microbore tubing. Attach the syringe to the luer end of the tubing.  
**CAUTION:** Use of other winged needles without microbore tubing, although compatible with the concentrate, will result in a larger retention of solution within the winged infusion set.

##### Rate of Administration

The rate of administration should be determined by the response and comfort of the patient; intravenous dosage administration rates of up to 225 IU/minute have been regularly tolerated without incident. When reconstituted as directed, *i.e.*, to approximately 100 IU/mL, Mononine® should be administered at a rate of approximately 2.0 mL per minute.

#### STORAGE

When stored at refrigerator temperature, 2°-8°C (36°-46°F), Coagulation Factor IX (Human), 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 30°C (86°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 diluent, double-ended needle for reconstitution, vented filter spike for withdrawal, winged infusion set and alcohol swabs. Factor IX activity in IU is stated on the label of each vial.

The following dosage forms are available:

- NDC 0053-7668-01 in 10 mL vials containing approximately 250 IU
- NDC 0053-7668-02 in 10 mL vials containing approximately 500 IU
- NDC 0053-7668-04 in 20 mL vials containing approximately 1,000 IU

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