

CSL Behring**Monoclote-P[®]**
Antihemophilic Factor (Human)
Factor VIII:C Pasteurized
Monoclonal Antibody Purified**R_x only****DESCRIPTION**

Monoclote-P[®], Antihemophilic Factor (Human), Factor VIII:C Pasteurized, Monoclonal Antibody Purified, is a sterile, stable, lyophilized concentrate of Factor VIII:C with reduced amounts of VWF:Ag and purified of extraneous plasma-derived protein by use of affinity chromatography. A murine monoclonal antibody to VWF:Ag is used as an affinity ligand to first isolate the Factor VIII Complex. Factor VIII:C is then dissociated from VWF:Ag, recovered, formulated and provided as a sterile lyophilized powder.^{1,2,3} The concentrate as formulated contains Albumin (Human) as a stabilizer, resulting in a concentrate with a specific activity between 4 and 10 units/mg of total protein. In the absence of this added Albumin (Human) stabilizer, specific activity has been determined to exceed 3000 units/mg of protein.⁴ Monoclote-P[®] has been prepared from pooled human plasma and is intended for use in therapy of classical hemophilia (Hemophilia A).

All Source Plasma used in the manufacture of this product was tested by FDA-licensed Nucleic Acid Tests (NAT) for HCV and HIV-1 and found to be nonreactive (negative).

An investigational NAT for HBV was also performed on all Source Plasma used in the manufacture of this product and found to be nonreactive (negative). The aim of the HBV test is to detect low levels of viral material, however, the significance of a nonreactive (negative) result has not been established.

This concentrate has been pasteurized by heating at 60°C for 10 hours in aqueous solution form during its manufacture in order to further reduce the risk of viral transmission.⁵ However, no procedure has been shown to be totally effective in removing viral infectivity from coagulant factor concentrates (see **CLINICAL PHARMACOLOGY** and **WARNINGS**).

Monoclote-P[®] is a highly purified preparation of Factor VIII:C. When stored as directed, it will maintain its labeled potency for the period indicated on the container and package labels.^{6,7}

Upon reconstitution of the 250, 500 and 1000 I.U. concentrates, a clear, colorless solution is obtained, containing 50 to 150 times as much Factor VIII:C as does an equal volume of plasma.

Upon reconstitution of the 1500 I.U. concentrate, a clear, colorless solution is obtained, containing 120 to 180 times as much Factor VIII:C as does an equal volume of plasma.

Each vial contains the labeled amount of antihemophilic factor (AHF) activity as expressed in terms of International Units (I.U.) of antihemophilic activity. One unit of antihemophilic activity is equivalent to that quantity of AHF present in one mL of normal human plasma. When reconstituted as recommended, the resulting solution contains approximately 300 to 450 millimoles of sodium ions per liter and has 2 to 3 times the tonicity of saline. It contains approximately 2-5 millimoles of calcium ions per liter, contributed as calcium chloride, approximately 1 to 2% Albumin (Human), 0.8% mannitol, and 1.2 mM histidine. The pH is adjusted with hydrochloric acid and/or sodium hydroxide. Monoclote-P[®] also contains trace amounts (≤ 50 ng per 100 I.U. of AHF) of the murine monoclonal antibody used in its purification (see **CLINICAL PHARMACOLOGY**).

Monoclote-P[®] is to be administered only intravenously.

CLINICAL PHARMACOLOGY

Factor VIII:C is the coagulant portion of the Factor VIII complex circulating in plasma. It is noncovalently associated with the von Willebrand protein responsible for von Willebrand factor activity. These two proteins have distinct biochemical and immunological properties and are under separate genetic control. Factor VIII:C acts as a cofactor for Factor IX to activate Factor X in the intrinsic pathway of blood coagulation.⁸ Hemophilia A, a hereditary disorder of blood coagulation due to decreased levels of Factor VIII:C, results in profuse bleeding into joints, muscles or internal organs as a result of a trauma. Monoclote-P[®] provides an increase in plasma levels of AHF, thereby enabling temporary correction of Hemophilia A bleeding.

Clinical evaluation of Monoclote-P[®] concentrate for its half-life characteristics in hemophilic patients showed it to be comparable to other commercially available Antihemophilic Factor (Human) concentrates. The mean half-life obtained from six patients was 17.5 hours with a mean recovery of 1.9 units/dl rise/U/kg.

The pasteurization process used in the manufacture of this concentrate has demonstrated *in vitro* inactivation of human immunodeficiency virus (HIV) and several model viruses. In two separate studies, HIV was reduced by $\geq 7.0 \log_{10}$ to an undetectable level and by $10.5 \log_{10}$, respectively. In addition to HIV, studies were also performed using three lipid containing model viruses and one non-lipid, encapsulated model virus. Vesicular stomatitis (VSV) was reduced by $\geq 6.79 \log_{10}$ to undetectable, Sindbis was reduced by $\geq 6.48 \log_{10}$ to

undetectable and Vaccinia was reduced by $\geq 5.36 \log_{10}$ to undetectable. Murine encephalomyocarditis (EMC), a non-lipid, encapsulated model virus, was reduced by $\geq 7.1 \log_{10}$ to undetectable.

Evidence of the capability of the purification and preparative steps used in the production of Monoclote-P[®] to reduce viral bioburden was obtained in studies involving the addition of known quantities of virus to cryoprecipitate. These studies were conducted using an earlier form of the concentrate which had not undergone liquid pasteurization (Monoclote[®], Antihemophilic Factor (Human), Monoclonal Antibody Purified, Factor VIII:C, Heat-Treated). These studies provide evidence of the viral removal potential of the purification and preparative steps of the manufacturing process (exclusive of heat treatment) which are common to both concentrates. In one study, the viruses used were human immunodeficiency virus (HIV), Sindbis virus, vesicular stomatitis virus (VSV) and pseudorabies virus (PsRV). A comparison of the cumulative mean reductions for all viruses tested with the individual values obtained in each experiment indicates that the combined effects of the manufacturing steps, which purify the Factor VIII:C and prepare the concentrate in a final sterile container as a lyophilized powder, contribute viral reduction capabilities of approximately 5 to 6 logs. In a separate study, aluminum hydroxide treatment followed by antibody affinity chromatography reduced vaccinia virus infectivity by 4.81 logs. These studies indicate that the purification and preparative steps of the manufacturing process are capable of providing a non-specific, viral reduction of approximately 5 to 6 logs, independent of the pasteurization process.

Monoclote-P[®] contains trace amounts of mouse protein⁹ (≤ 50 ng per 100 I.U. of AHF). In a study using an earlier form of the concentrate which had not undergone pasteurization (Monoclote[®]), a number of patients seronegative for Anti-HIV-1 were monitored to determine whether they would develop antibody or experience adverse reactions as a result of repeated exposure. These patients were treated on multiple occasions. Pre-study serum measurements of 27 patients for human anti-mouse IgG showed that, prior to treatment, 6 of them had either detectable antibody to mouse proteins or cross-reactive proteins. These patients continued to demonstrate similar or lower antibody levels during the study. Of the remaining 21 patients, 6 were shown to have low antibody levels on one or more occasions. In no case was observance of low antibody level associated with an anamnestic response or with any clinical adverse reaction. Patients were observed for time periods ranging from 2 to 30 months.

The viral safety of Monoclote-P[®] has been evaluated in two open-label studies using patients (aged 1 day to 20 years) with moderate to severe hemophilia A previously unexposed to blood or blood products. Thirty patients received Monoclote-P[®] therapy for 5 to 34 months as necessary according to the normal practices of the treatment center. These patients were followed for serum ALT elevations and a range of viral serologies. Six patients received another blood product prior to or during the study. Twenty-four patients were evaluable for assessment of viral safety of Monoclote-P[®]. No patients seroconverted to HIV, hepatitis

nonA/nonB, or hepatitis B. Factor VIII:C inhibitors developed in 7 patients (23%) with 3 being high (>10 BU) titer.

INDICATIONS AND USAGE

Monoclote-P[®] is indicated for treatment of classical hemophilia (Hemophilia A). Affected individuals frequently require therapy following minor accidents. Surgery, when required in such individuals, must be preceded by temporary corrections of the clotting abnormality. Surgical prophylaxis in severe AHF deficiency can be accomplished with an appropriately-dosed pre-surgical IV bolus of Monoclote-P[®] followed by intermittent maintenance doses (see **DOSAGE AND ADMINISTRATION**).

Monoclote-P[®] is not effective in controlling the bleeding of patients with von Willebrand's disease.

CONTRAINDICATIONS

Known hypersensitivity to mouse protein is a contraindication to Monoclote-P[®].

WARNINGS

Monoclote-P[®] is made from human blood. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Monoclote-P[®] 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. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current viral infections and inactivating and/or removing certain viruses during manufacture (see **DESCRIPTION** section for viral reduction measures). The manufacturing procedure for Monoclote-P[®] includes processing steps designed to reduce further the risk of viral transmission. Stringent procedures utilized at plasma collection centers, plasma testing laboratories, and fractionation facilities are designed to reduce the risk of viral transmission. The primary viral reduction step of the Monoclote-P[®] manufacturing process is the heat treatment of the purified, stabilized aqueous solution at 60°C for 10 hours. In addition, the purification procedure (several precipitation steps) used in the manufacture of Monoclote-P[®] also provides viral reduction capacity. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus the risk of transmission of infectious agents can not 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 healthcare provider to CSL Behring at 800-504-5434 (in the U.S. or Canada).

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections (see **Information For Patients**).

PRECAUTIONS

General - Most Antihemophilic Factor (Human) concentrates contain naturally occurring blood group specific antibodies. However, the processing of Monoclade-P® significantly reduces the presence of blood group specific antibodies in the final product. Nevertheless, when large or frequently repeated doses of product are needed, patients should be monitored by means of hematocrit and direct Coombs tests for signs of progressive anemia.

Formation of Antibodies to Mouse Protein - Although no hypersensitivity reactions have been observed, because Monoclade-P® contains trace amounts of mouse protein (≤ 50 ng per 100 I.U. of AHF), the possibility exists that patients treated with Monoclade-P® may develop hypersensitivity to the mouse proteins.

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.

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.

Although the overwhelming number of hepatitis A and parvovirus B19 cases are community acquired, there have been reports of these infections associated with the use of some plasma-derived products. Therefore, physicians should be alert to the potential symptoms of parvovirus B19 and hepatitis A infections and inform patients under their supervision receiving plasma derived products to report potential symptoms promptly.

Symptoms of parvovirus B19 include fever, drowsiness, chills and runny nose followed 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 physicians if such symptoms occur.

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

Pediatric Use – The safety and effectiveness of Monoclade-P® for the treatment of hemophilia A has been demonstrated in 33 pediatric patients. As in adults, pediatric patients should be dosed based upon weight (see **DOSAGE AND ADMINISTRATION**).

Geriatric Use - Clinical studies of Monoclate-P® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Dosing should be appropriate to the clinical situation.

ADVERSE REACTIONS

Products of this type are known to cause allergic reactions, mild chills, nausea or stinging at the infusion site. In some cases, inhibitors of FVIII may occur.

DOSAGE AND ADMINISTRATION

Monoclate-P® is for intravenous administration only. As a general rule 1 unit of AHF activity per kg will increase the circulating AHF level by 2%.¹⁰ The following formula¹⁰ provides a guide of dosage calculations for both adult and pediatric patients:

$$\text{Number of AHF I.U. Required} = \text{Body weight (in kg)} \times \text{desired Factor VIII increase (\% normal)} \times 0.5$$

Although dosage must be individualized according to the needs of the patient (weight, severity of hemorrhage, presence of inhibitors), the following general dosages are suggested.¹¹

1. **MILD HEMORRHAGES** - Minor hemorrhagic episodes will generally subside with a single infusion if a level of 30% or more is attained.
2. **MODERATE HEMORRHAGE AND MINOR SURGERY** - For more serious hemorrhages and minor surgical procedures, the patient's Factor VIII level should be raised to 30-50% of normal, which usually requires an initial dose of 15-25 I.U. per kg. If further therapy is required a maintenance dose is 10-15 I.U. per kg every 8-12 hours.
3. **SEVERE HEMORRHAGE** - In hemorrhages near vital organs (neck, throat, subperitoneal) it may be desirable to raise the Factor VIII level to 80-100% of normal which can be achieved with an initial dose of 40-50 I.U. per kg and a maintenance dose of 20-25 I.U. per kg every 8-12 hours.
4. **MAJOR SURGERY** - For surgical procedures a dose of AHF sufficient to achieve a level 80-100% of normal should be given an hour prior to surgery. A second dose, half the size of the priming dose, should be given five hours after the first dose. Factor VIII levels should be maintained at a daily minimum of at least 30% for a

period of 10-14 days postoperatively. Close laboratory control to maintain AHF plasma levels deemed appropriate to maintain hemostasis is recommended.

Reconstitution

1. Warm both the diluent and Monoclote-P® 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 Monoclote-P® vial. Direct the diluent, which will be drawn in by vacuum, over the entire surface of the Monoclote-P® 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 Monoclote-P® 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, Monoclote-P® should be administered within three hours after reconstitution.
7. Parenteral drug preparations should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Administration

CAUTION: This kit contains two devices, a stainless steel 5 micron filter needle, individually labeled as a 5 micron filter needle and contained in a separate blister pack, and an all plastic 5 micron vented filter spike which is supplied with the four-item administration components blister pack, either of which may be used to withdraw the reconstituted product for administration. The withdrawal directions specific for each of these alternate devices must be followed exactly for whichever device is chosen for use as described below. Product loss or inability to withdraw product will result if the improper instructions are followed.

- A. Administration using the stainless steel filter needle for withdrawal
(This item is individually packaged in a separate, labeled blister pack.)

Intravenous Injection

Plastic disposable syringes are recommended with Monoclote-P[®] solution. The ground glass surfaces of all-glass syringes tend to stick with solutions of this type.

1. Using aseptic technique, attach the filter needle to a sterile disposable syringe.
2. Draw air into the syringe equal to or greater than the contents of the vial.
3. Insert the filter needle into the stopper of the Monoclote-P[®] vial, invert the vial, position the filter needle above the level of the liquid and inject all of the air into the vial.
4. Pull the filter needle back down below the level of the liquid until the tip is at the inside edge of the stopper.
5. Withdraw the reconstituted solution into the syringe being careful to always keep the tip of the needle below the level of the liquid.

CAUTION: Failure to inject air into the vial, or allowing air to pass through the filter needle while filling the syringe with reconstituted solution, may cause the needle to clog.

6. Discard the filter needle. 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.

7. **Administer solution intravenously at a rate (approximately 2 mL/minute) comfortable to the patient.**

- B. Administration using the all plastic vented filter spike for withdrawal
(This spike is supplied in the four-item Administration Components pack.)

Intravenous Injection

Plastic disposable syringes are recommended with Monoclote-P[®] solution. The ground glass surfaces of all-glass syringes tend to stick with solutions of this type.

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

CAUTION: DO NOT INJECT AIR INTO THE MONOCLATE-P[®] 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.

CAUTION: The use of other, non-vented filter needles or spikes without the proper procedure may result in an air lock and prevent the complete transfer of the concentrate.

2. Insert the vented filter spike into the stopper of the Monoclote-P[®] 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.

5. **Administer solution intravenously at a rate (approximately 2 mL/minute) comfortable to the patient.**

STORAGE

When stored at refrigerator temperature, 2-8°C (36-46°F), Monoclote-P[®] is stable for the period indicated by the expiration date on its label. Within this period, Monoclote-P[®] may be stored at room temperature not to exceed 25°C (77°F), for up to 6 months.

Avoid freezing which may damage container for the diluent.

HOW SUPPLIED

Monoclate-P[®] is supplied in a single dose vial with diluent, double-ended needle for reconstitution, vented filter spike for withdrawal, filter needle for withdrawal, winged infusion set and alcohol swabs. I.U. activity is stated on the label of each vial.

The following strengths are available:

NDC 0053-7656-01 in 10 mL vials containing approximately 250 I.U. (Dosage – LOW)
NDC 0053-7656-02 in 10 mL vials containing approximately 500 I.U. (Dosage – MID)
NDC 0053-7656-04 in 20 mL vials containing approximately 1000 I.U. (Dosage – HIGH)
NDC 0053-7656-05 in 20 mL vials containing approximately 1500 I.U. (Dosage – Super High)

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