

PRESCRIBING INFORMATION
ANTIHEMOPHILIC FACTOR (HUMAN)
MONOCLATE-P®
FACTOR VIII:C PASTEURIZED,
MONOCLONAL ANTIBODY PURIFIED

AVENTIS BEHRING L.L.C.
Kankakee, Illinois 60901, U.S.A.
U.S. License No. 1281



Aventis Behring

Rx only
DESCRIPTION

Antihemophilic Factor (Human), Monoclolate-P®, 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 5 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 Monoclolate-P® has been prepared from pooled human plasma and is intended for use in therapy of classical hemophilia (Hemophilia A).

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 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**.)

Monoclolate-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.^{8,9}

Upon reconstitution, a clear, colorless solution is obtained, containing 50 to 150 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 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. Monoclolate-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**).

Monoclolate-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.⁶ Hemophilia A, an 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. Monoclolate-P® provides an increase in plasma levels of AHF, thereby enabling temporary correction of hemophilia A bleeding.

Clinical evaluation of Monoclolate-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 ≥7.0 log₁₀ to an undetectable level and by 10.5 log₁₀, 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 ≥6.79 log₁₀ to undetectable, Sindbis was reduced by ≥6.48 log₁₀ to undetectable and Vaccinia was reduced by ≥5.36 log₁₀ to undetectable. Murine encephalomyocarditis (EMC), a non-lipid, encapsulated model virus, was reduced by ≥7.1 log₁₀ to undetectable.

Evidence of the capability of the purification and preparative steps used in the production of Monoclolate-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 (Antihemophilic Factor (Human), Monoclolate®, 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.

Monoclolate-P® contains trace amounts of mouse protein⁷ (≤50 ng per 100 I.U. of AHF). In a study using an earlier form of the concentrate which had not undergone pasteurization (Monoclolate®), 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 observation 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.

INDICATIONS AND USAGE

Monoclolate-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. Presurgical correction of severe AHF deficiency can be accomplished with a small volume of Monoclolate-P®.

Monoclolate-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 Monoclolate-P®.

WARNINGS

This product is prepared from pooled human plasma which may contain the causative agents of hepatitis and other viral diseases. Prescribed manufacturing procedures utilized at the plasma collection centers, plasma testing laboratories, and the fractionation facilities are designed to reduce the risk of transmitting viral infection. However, the risk of viral infectivity from this product cannot be totally eliminated. Accordingly, the benefits and risks of treatment with this concentrate should be carefully assessed prior to use.

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly nonA, nonB hepatitis.

Because Monoclolate-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.

PRECAUTIONS

General – Most Antihemophilic Factor (Human) concentrates contain naturally occurring blood group specific antibodies. However, the processing of Monoclolate-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 Monoclolate-P® contains trace amounts of mouse protein (≤50 ng per 100 I.U. of AHF), the possibility exists that patients treated with Monoclolate-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.

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

GERIATRIC USE – Clinical studies of Monoclolate-P® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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.

DOSAGE AND ADMINISTRATION

Monoclolate-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 formula provides a guide of dosage calculations:

$$\text{Number of AHF I.U. Required} = \text{Body weight (in kg)} \times \frac{\text{desired Factor VIII increase (\% normal)}}{0.5^{10}}$$

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 Monoclolate-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 Monoclolate-P® vial. Direct the diluent, which will be drawn in by vacuum, over the entire surface of the Monoclolate-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 Monoclolate-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, Monoclolate-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 Monoclolate-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 Monoclolate-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 Monoclolate-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

Monoclote-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.

REFERENCES

1. W. Terry, A. Schreiber, C. Tarr, M. Hrinda, W. Curry and F. Feldman, Human Factor VIII:C Produced Using Monoclonal Antibodies, in *Research in Clinic and Laboratory*, Vol. XVI, (#1), 202 (1986) from the XVIII International Congress of the World Federation of Hemophilia.
2. A.B. Schreiber, The Preclinical Characterization of Monoclote Factor VIII C Antihemophilic Factor Human, *Semin Hematol*, 25 (2 Suppl. 1), 1988, pp. 27-32.
3. E. Berntorp and I.M. Nilsson, Biochemical Properties of Human Factor VIII C Monoclote Purified Using Monoclonal Antibody to VWF, *Thromb Res O* (Suppl. 7), 1987, p. 60, from the Satellite Symposia of the Xth International Congress on Thrombosis and Haemostasis, Brussels, Belgium, July 11, 1987.
4. S. Chandra, C.C. Huang, R.L. Weeks, K. Beatty and F. Feldman, Purity of a Factor VIII:C Preparation (Monoclote) Manufactured by Monoclonal Immunoaffinity Chromatography Technique, from the XVIII International Congress of the World Federation of Hemophilia, May 1988.
5. B. Spire, D. Dormont, F. Barre-Sinoussi, L. Montagnier, and J.C. Chermann, Inactivation of Lymphadenopathy Associated Virus by Heat, Gamma Rays, and Ultraviolet Light, *Lancet*, Jan. 26, 1985, p. 188.
6. L.W. Hoyer, The Factor VIII Complex: Structure and Function, *Blood* 58 (1981), p. 1.
7. F. Feldman, S. Chandra, R. Kleszynski, C.C. Huang and R.L. Weeks, Measurement of Murine Protein Levels in Monoclonal Antibody Purified Coagulation Factor, from the XVIII International Congress of the World Federation of Hemophilia, May 1988.
8. F. Feldman, R. Kleszynski, L. Ho, R. Kling, S. Chandra and C.C. Huang, Validation of Coagulation Test Methods for Evaluation of Monoclote (Factor VIII:C) Potencies, from the XVIII International Congress of the World Federation of Hemophilia, May 1988.
9. S. Chandra, C.C. Huang, L. Ho, R. Kling, R.L. Weeks and F. Feldman, Studies on the Stability of Factor VIII:C (Monoclote) in Lyophilized and Solution Form, from the XVIII International Congress of the World Federation of Hemophilia, May 1988.
10. C.F. Abilgaard, J.V. Simone, J.J. Corrigan, *et al.*, Treatment of Hemophilia with Glycine—Precipitated Factor VIII, *New Eng J Med*, 275 (1966), p. 471.
11. C.K. Kasper, Hematologic Care, *Comprehensive Management of Hemophilia*, ed. Boone, D.C., Philadelphia, F.A. Davis Co., (1976) pp. 2-20.

BIBLIOGRAPHY

Hershman, R.J., Naconti, S.B., and Shulman, N.R. Prophylactic Treatment of Factor VIII Deficiency. *Blood* 35, (1970), p. 189.

Kasper, C.K., Dietrich, S.I. and Rapaport, S.K. Hemophilia Prophylaxis in Factor VIII Concentrate. *Arch. Int. Med.* 125, (1970), p. 1004.

Biggs, R., ed. The Treatment of Hemophilia A and B and von Willebrands Disease. Oxford: Blackwell, 1978.

Fulcher, C.A., Zimmerman, T.S., Characterization of the Human Factor VIII Procoagulant Protein With a Heterologous Precipitating Antibody. *Proc. Natl. Acad. Sci.* 79, (1982), pp. 1648-1652.

Levine, P.H., Factor VIII C Purified from Plasma Via Monoclonal Antibodies Human Studies. *Semin Hematol* 25, (2 Suppl. 1), 1988, pp. 38-41.