Antihemophilic Factor (Human) Monoclate-P®

Factor VIII:C Pasteurized Monoclonal Antibody Purified

DESCRIPTION
Antihemophilic Factor (Human), Monoclate-P®, Factor VIII:C Pasteurized, Monoclonal Antibody Purified, is a sterile, stable, lyophilized concentrate of Factor VIII:C with reduced amounts of WVF-Ag and purified of extraneous plasma-derived protein by use of affinity chromatography. A murine monoclonal antibody to WVF-Ag is used as an affinity ligand to first isolate the Factor VIII Complex. Factor VIII:C is then dissociated from WVF-Ag, recovered, formulated and provided as a sterile lyophilized powder. The concentrate has 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.

Monoclate-P® contains trace amounts of mouse protein (≤50 ng per 100 I.U. of AHF). In a study using an earlier form of the concentrate which had not undergone pasteurization (Monoclate®), a number of patients seroconverted 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 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 Monoclate-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 Monoclate-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 Monoclate-P®. No patients seroconverted to HIV, hepatitis nonA/nonB, or hepatitis B. Factor VIII:C inhibitors developed in 7 patients (23%) with being high (>10 BU) titer.

INDICATIONS AND USAGE
Monoclate-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 Monoclate-P® followed by intermittent maintenance doses (see DOSAGE AND ADMINISTRATION). Monoclate-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 Monoclate-P®.

WARNINGS
Monoclate-P® is made from human blood. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Monoclate-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 Monoclate-P® includes processing steps designed to reduce further the risk of viral transmission. Stingent 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 Monoclate-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 Monoclate-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 1-866-915-6956 (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 - MostAntihemophilic Factor (Human) concentrates contain naturally occurring blood group specific antibodies. However, the processing of Monoclate-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 hemocrit and direct Coombs tests for signs of progressive anemia.

Formation of Antibodies to Mouse Protein - Although no hypersensitivity reactions have
been observed, because Monoclate-P® contains trace amounts of mouse protein (≤50 ng per 100 I.U. of AHF), the possibility exists that patients treated with Monoclate-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 Monoclate-P®. It is also not known whether Monoclate-P® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Monoclate-P® should be given to a pregnant woman only if clearly needed.

**Pediatric Use** – The safety and effectiveness of Monoclate-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 injection site. In some cases, inhibitors of VIII 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%. The following formula provides a guide of dosage calculations for both adult and pediatric patients:

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

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.

1. **MILD HEMORRHAGES** - Minor hemorrhagic episodes will generally subside with a single infusion if a level of 30% of 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 Monoclate-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 antisepsic 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 Monoclate-P® vial. Direct the diluent, which will be drawn in by vacuum, over the entire surface of the Monoclate-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 Monoclate-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, Monoclate-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 Monoclate-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 Monoclate-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 Monoclate-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 MONOCRATE-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 Monoclate-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), Monoclate-P® is stable for the period indicated by the expiration date on its label. Within this period, Monoclate-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 Sterile Water for Injection, USP, double-ended needle for reconstitution, vented filter spike for withdrawal, filter needle for withdrawal, winged infusion set and alcohol swabs. Factor VIII activity in IU is stated on the label of each vial.
Each product package consists of the following:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Approximate FVIII Activity (IU)</th>
<th>Component</th>
</tr>
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<tbody>
<tr>
<td>0053-7631-02</td>
<td>250 (LOW)</td>
<td>Carton (kit) containing one vial of Monoclate-P® [NDC 0053-7641-01], one 2.5 mL vial of Sterile Water for Injection, USP (diluent) [NDC 0053-7653-02], one double-ended needle for reconstitution, one vented filter spike for withdrawal, one filter needle for withdrawal, one winged infusion set, and alcohol swabs.</td>
</tr>
<tr>
<td>0053-7632-02</td>
<td>500 (MID)</td>
<td>Carton (kit) containing one vial of Monoclate-P® [NDC 0053-7642-01], one 5 mL vial of Sterile Water for Injection, USP (diluent) [NDC 0053-7653-05], one double-ended needle for reconstitution, one vented filter spike for withdrawal, one filter needle for withdrawal, one winged infusion set, and alcohol swabs.</td>
</tr>
<tr>
<td>0053-7633-02</td>
<td>1000 (HIGH)</td>
<td>Carton (kit) containing one vial of Monoclate-P® [NDC 0053-7643-01], one 10 mL vial of Sterile Water for Injection, USP (diluent) [NDC 0053-7653-10], one double-ended needle for reconstitution, one vented filter spike for withdrawal, one filter needle for withdrawal, one winged infusion set, and alcohol swabs.</td>
</tr>
<tr>
<td>0053-7634-02</td>
<td>1500 (SUPER HIGH)</td>
<td>Carton (kit) containing one vial of Monoclate-P® [NDC 0053-7644-01], one 10 mL vial of Sterile Water for Injection, USP (diluent) [NDC 0053-7653-10], one double-ended needle for reconstitution, one vented filter spike for withdrawal, one filter needle for withdrawal, one winged infusion set, and alcohol swabs.</td>
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**REFERENCES**


**BIBLIOGRAPHY**


Manufactured by:

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US License No. 1767

Revised February, 2014
12810-08