

Baxter

HEMOFIL M

Antihemophilic Factor (Human) Method M, Monoclonal Purified

DESCRIPTION

HEMOFIL M, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified is a sterile, nonpyrogenic, dried preparation of antihemophilic factor (Factor VIII:C AHF) with a specific activity range of 2 to 15 AHF International Units/mg of total protein. When reconstituted with the appropriate volume of diluent, it contains approximately 12.5 mg/mL Albumin (Human), 1.5 mg/mL polyethylene glycol (3350), 0.055 M histidine and 0.030 M glycine as stabilizing agents. In the absence of the added Albumin (Human), the specific activity is approximately 2,000 AHF International Units/mg of protein. It also contains trace amounts of mouse protein, less than 10 mg/100 AHF activity units. **See CLINICAL PHARMACOLOGY.**

HEMOFIL M AHF is prepared by the Method M process from pooled human plasma by immunoaffinity chromatography utilizing a murine monoclonal antibody to Factor VIII:C, followed by an ion exchange chromatography step for further purification. Method M also includes an organic solvent [tri(n-butyl)phosphate] and detergent (octoxynol 9) virus inactivation step designed to reduce the risk of transmission of hepatitis and other viral diseases. However, no procedure has been shown to be totally effective in removing viral infectivity from coagulation factor products.

Each bottle of **HEMOFIL M** AHF is labeled with the AHF activity expressed in International Units per bottle, which is referenced to the WHO International Standard.

HEMOFIL M AHF must be administered intravenously.

CLINICAL PHARMACOLOGY

Antihemophilic Factor (AHF) is a protein found in normal plasma which is necessary for clot formation. The administration of **HEMOFIL M** AHF provides an increase in plasma levels of AHF and can temporarily correct the coagulation defect of patients with hemophilia A (classical hemophilia). The administration of Antihemophilic Factor (AHF) will also correct deficiencies

caused by circulating inhibitors when the inhibitor level does not exceed 10 Bethesda Units per mL.

The half-life of **HEMOFIL M**, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified administered to Factor VIII deficient patients has been shown to be 14.8 ± 3.0 hours.

Use of an organic solvent [tri(n-butyl)phosphate; TNBP] in the manufacture of Antihemophilic Factor (Human) has little or no effect on AHF activity, while lipid enveloped viruses, such as hepatitis B and human immunodeficiency virus (HIV) are inactivated.¹ Prince, *et al*, report inactivation of at least 10,000 Chimpanzee Infectious Doses (CID-50) of hepatitis B virus, 10,000 CID-50 of hepatitis non A, non B virus, and 30,000 Tissue Culture Infectious Doses of HIV with TNBP/detergent treatment during manufacture of an Antihemophilic Factor (Human) concentrate.²

The effectiveness of the Method M organic solvent/detergent inactivation step in reducing viral infectivity was assessed *in vitro* by using marker viruses. When known quantities of Sindbis virus, Vesicular Stomatitis virus, and Pseudorabies virus were added during manufacture, this step was shown to inactivate 3 to 4 logs of these viruses. The infectivity of HIV seeded into cryoprecipitate was reduced by greater than 4 logs almost instantaneously by the organic solvent/detergent step. In four other experiments, the concentration of both enveloped and non-enveloped viruses were decreased approximately 4 logs during the immunoaffinity chromatography step.

HEMOFIL M AHF was administered to 11 patients previously untreated with Antihemophilic Factor (Human). They have shown no signs of hepatitis or HIV infection following 3 to 9 months of evaluation. An ongoing study of 25 patients treated with **HEMOFIL M AHF** and monitored for 3 to 6 months has demonstrated no evidence of antibody response to mouse protein. More than 1,000 infusions of **HEMOFIL M AHF** have been administered during the clinical trials with no significant reactions. Reported events included a single episode each of chest tightness, fuzziness and dizziness and one patient reported an unusual taste after each infusion.

INDICATIONS AND USAGE

The use of **HEMOFIL M AHF** is indicated in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes.

HEMOFIL M AHF can be of significant therapeutic value in patients with acquired Factor VIII inhibitors not exceeding 10 Bethesda Units per mL.³ However, in such cases, the dosage should be controlled by frequent laboratory determinations of circulating Factor VIII.

HEMOFIL M AHF is not indicated in von Willebrand's disease.

CONTRAINDICATIONS

Known hypersensitivity to mouse protein is a contraindication to the use of **HEMOFIL M**, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified.

WARNINGS

This product is prepared from pooled human plasma which have been individually tested and found nonreactive for hepatitis B surface antigen and negative for antibody to human immunodeficiency virus (HIV) by FDA approved tests, and have been shown to have alanine aminotransferase (ALT) levels not exceeding two times the upper limit of normal.

Other screening procedures are used to reduce the risk of transmitting viral infection. However, testing methods are not sensitive enough to detect units of potentially infectious plasma and treatment methods have not been shown to be totally effective in eliminating viral infectivity from this product.

Individuals who have not received multiple infusions of blood or plasma products are likely to develop signs and/or symptoms of certain viral infections, especially non A, non B hepatitis, when treated with coagulant factor products. As indicated under **CLINICAL PHARMACOLOGY**, however, a group of such patients treated with **HEMOFIL M AHF** did not demonstrate signs or symptoms of non A, non B hepatitis over observation periods ranging from 3 to 9 months.

PRECAUTIONS

Identification of the clotting defect as a Factor VIII deficiency is essential before the administration of **HEMOFIL M AHF** is initiated. No benefit may be expected from this product in treating other deficiencies.

The processing of **HEMOFIL M AHF** 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 **HEMOFIL M AHF** contains trace amounts of mouse protein (less than 10 ng/100 AHF activity units), the possibility exists that patients treated with this product may develop hypersensitivity to the mouse proteins.

The pulse rate should be determined before and during administration of Antihemophilic Factor (Human). Should a significant increase occur, reducing the rate of administration or temporarily halting the injection usually allows the symptoms to disappear promptly.

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 product and contact their physician if these symptoms occur.

Laboratory Tests

Although dosage can be estimated by the calculations which follow, it is strongly recommended that whenever possible, appropriate laboratory tests be performed on the patient's plasma at suitable intervals to assure that adequate AHF levels have been reached and are maintained.

If the AHF content of the patient's plasma fails to reach expected levels or if bleeding is not controlled after apparently adequate dosage, the presence of inhibitor should be suspected. By appropriate laboratory procedures, the presence of inhibitor can be demonstrated and quantified in terms of AHF units neutralized by each mL of plasma or by the total estimated plasma volume. If the inhibitor is at low levels (i.e., <10 Bethesda Units/mL) after administration of sufficient AHF units to neutralize the inhibitor, additional AHF units will elicit the predicted response.

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with **HEMOFIL M**, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified. It is not known whether **HEMOFIL M** AHF can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. **HEMOFIL M** AHF should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Allergic reactions may be encountered from the use of **HEMOFIL M** AHF preparations. See **Information for Patients**.

The protein in greatest concentration in **HEMOFIL M** AHF is Albumin (Human). Reactions associated with albumin are extremely rare, although nausea, fever, chills or urticaria have been reported.

DOSAGE AND ADMINISTRATION

Each bottle of **HEMOFIL M** AHF is labeled with the Factor VIII content expressed in International Units per bottle. This potency assignment is traceable to the World Health Organization International Standard.

The following formulas can be used to calculate the appropriate dose required for a given response (I) or the response to be expected from a given dose (II). These dosage formulas are presented as references and guidelines. The amount of Antihemophilic Factor (Human) that an individual haemophiliac requires for normal hemostasis varies with the circumstances and with the patient. Exact dosage determinations should be based on the medical judgment of the physician

regarding circumstances, condition of the patient, degree of Factor VIII deficiency and the level of Factor VIII to be achieved.

I. Units required =
body weight (kg) x 0.4 units/kg x desired AHF increase (% of normal)

Example: 70 kg x 0.4 units/kg x 50% = 1,400 units

II Expected AHF increase (% of normal) =

$$\frac{\text{units administered}}{\text{body weight (kg)} \times 0.4 \text{ units/kg}}$$

Example: $\frac{1,400 \text{ units}}{70 \text{ kg} \times 0.4 \text{ units/kg}} = 50\%$

The response factor used in the preceding formulas (0.4 units/kg) was based on the work of Shanbrom and Thelin with adults.⁴ Abildgaard, *et al*, in work with boys 8 months to 14 years of age, reported data from which a factor of 0.5 units/kg can be calculated.⁵

- A. Minor hemorrhagic episodes will generally subside with a single infusion if an AHF level of 30% or more is attained.
- B. For more serious hemorrhages, an AHF level of 35 to 50% of normal should be obtained for optimum clot formation.
- C. In surgery, the initial dose of **HEMOFIL M**, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified calculated to achieve a level of 80 to 100% of normal, should be given an hour before the procedure. A second dose of **HEMOFIL M** AHF half the size of the priming dose should be given five hours after the priming dose. If several units of blood were lost during the operation, a third dose of **HEMOFIL M** AHF should be given when the patient reaches the recovery room. AHF level should be maintained at a daily minimum of at least 30% for a healing period of 100 to 14 days.⁶

Other dosage regimens have been proposed, such as that of Hilgartner⁷, which outlines dosage according to the various types of bleeding episodes, and Schimpf, *et al*,⁸ which describes continuous maintenance therapy.

Reconstitution: Use Aseptic Technique

1. Bring **HEMOFIL M** AHF (dry concentrate) and Sterile Water for Injection, USP, (diluent) to room temperature.
2. Remove caps from concentrate and diluent bottles to expose central portion of rubber stoppers.
3. Cleanse stoppers with germicidal solution.
4. Remove protective covering from one end of double-ended needle and insert exposed needle through diluent stopper.
5. Remove protective covering from other end of double-ended needle. Invert diluent bottle over upright **HEMOFIL M** AHF bottle, then rapidly insert free end of the needle through the **HEMOFIL M** AHF bottle stopper

at its center. The vacuum in the **HEMOFIL M AHF** bottle will draw in the diluent.

6. Disconnect the two bottles by removing needle from diluent bottle stopper, then remove needle from **HEMOFIL M AHF** bottle. Swirl gently until all material is dissolved. Be sure that **HEMOFIL M AHF** is completely dissolved, otherwise active material will be removed by the filter.

Note: Do not refrigerate after reconstitution.

Administration: Use Aseptic Technique

Administer at room temperature.

HEMOFIL M AHF should be administered not more than three hours after reconstitution.

Intravenous Syringe Injection

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

Plastic syringes are recommended for use with this product. The ground glass surface of all-glass syringes tend to stick with solutions of this type.

1. Attach filter needle to a disposable syringe and draw back plunger to admit air into syringe.
2. Insert needle into reconstituted **HEMOFIL M AHF**.
3. Inject air into bottle and then withdraw the reconstituted material into the syringe.
4. Remove and discard the filter needle from the syringe; attach a suitable needle and inject intravenously as instructed under **Rate of Administration**.
5. If the same patient is to receive more than one bottle of **HEMOFIL M**, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified, the contents of two bottles may be drawn into the same syringe by drawing up each bottle through a separate, unused filter needle. This practice lessens the loss of **HEMOFIL M AHF**.

Please note, filter needles are intended to filter the contents of a single bottle of **HEMOFIL M AHF**.

Rate of Administration

Preparations of **HEMOFIL M AHF** can be administered at a rate of up to 10 mL per minute with no significant reactions.

As a precaution, the pulse rate should be determined before and during administration of **HEMOFIL M AHF**. Should a significant increase occur, reducing the rate of administration or, temporarily halting the injection, usually allows the symptoms to disappear promptly.

HOW SUPPLIED

HEMOFIL M AHF is available as single dose bottles. Each bottle is labeled with the potency in International Units, and is packaged together with 10 mL of Sterile Water for Injection, USP, a double-ended needle, and a filter needle.

STORAGE

HEMOFIL M, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified should be stored under refrigeration (2 to 8°C, 36 to 46°F). Avoid freezing to prevent damage to the diluent bottle.

REFERENCES

1. Horowitz B, Wiebe ME, Lippin A, *et al*: Inactivation of viruses in labile blood derivatives: I. Disruption of lipid enveloped viruses by tri(n-butyl)phosphate detergent combinations. **Transfusion** **25**:516-522, 1985
2. Prince AM, Horowitz B, Brotman B: Sterilization of hepatitis and HTLV-III viruses by exposure to tri(n-butyl)phosphate and sodium cholate. **Lancet** **I**:706-710, 1986
3. Brinkhous KM, Shanbrom E, Roberts HR, *et al*: A new high potency glycine-precipitated Antihemophilic Factor (AHF) concentrate; Treatment of classical hemophilia and hemophilia with inhibitors. **JAMA** **205**:613-617, 1968
4. Shanbrom E, Thelin GM: Experimental prophylaxis of severe hemophilia with a Factor VIII concentrate. **JAMA** **208**:1853-1856, 1969
5. Abildgaard CF, Simone JV, Corrigan JJ, *et al*: Treatment of hemophilia with glycine-precipitated Factor VIII. **New Eng J Med** **275**:471-475, 1966
6. Kasper CK: Hematologic care, in **Comprehensive Management of Hemophilia**. Boone DC (ed), Philadelphia, F.A. Davis Co., 1976, pp 3-17
7. Hilgartner MW: Factor replacement therapy in **Hemophilia in the Child and Adult**, ed. New York, Masson Publishing, USA, Inc., 1982, pp 63-84
8. Schimpf K, Rothmann P, Zimmerman K: Factor VIII doses in prophylaxis of hemophilia A; A further controlled study, in **Proc XIth Cong W.F.H.** Kyoto, Japan, Academic Press, 1976, pp 363-366

Baxter and Hemofil are trademarks of Baxter International, Inc., and are registered in the U.S. Patent and Trademark office.

Manufactured by:

Baxter Healthcare Corporation

Westlake Village, CA 91362 USA

U.S. License No. 140

Imported by:

Baxter Corporation

Toronto, Ontario, Canada