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, Factor VIII:C, AHF) in concentrated form with a specific activity range of 2 to 20 AHF International Units/mg of total protein. **HEMOFIL** M contains a maximum of 12.5 mg/mL Albumin, and per AHF International Unit, 0.07 mg polyethylene glycol (3350), 0.39 mg histidine, 0.1 mg glycine as stabilizing agents, not more than 0.1 ng mouse protein, 18 ng organic solvent (tri-n-butyl phosphate) and 50 ng detergent (octoxynol 9). In the absence of the added Albumin (Human), the specific activity is approximately 2,000 AHF International Units/mg of protein. 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. Source material may be provided by other US licensed manufacturers. **HEMOFIL** M AHF 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 is to be administered only 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 **HEMOFIL** M 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]

In vitro studies demonstrate that the **HEMOFIL** M AHF, manufacturing process provides for significant viral reduction. These studies, summarized in Table 1, demonstrate virus clearance during the **HEMOFIL** M AHF manufacturing process using human immunodeficiency virus, Type 1 (HIV-1); bovine viral diarrhea virus (BVD), a model for lipid enveloped RNA viruses, such as hepatitis C virus (HCV); pseudorabies virus (PRV), a model for lipid enveloped DNA viruses, such as herpes; porcine parvovirus (PPV), a model for non-lipid enveloped DNA viruses, such as human parvovirus B19; and hepatitis A virus (HAV), a model for non-lipid enveloped RNA viruses. These reductions are achieved through a combination of process chemistry, partitioning and/or inactivation during solvent/detergent treatment, immunoaffinity chromatography, Q-Sepharose column chromatography and lyophilization.

Table 1
***In Vitro* Virus Clearance During the Manufacture of HEMOFIL M AHF**

Process Step Evaluated	Virus Clearance, log_{10}				
	Lipid-enveloped			Non-Lipid enveloped	
	HIV-1	BVD	PRV	PPV	HAV
Solvent/Detergent Treatment	10.3	3.8	4.3	*	*
Immunoaffinity Chromatography	N.A.**	N.A.**	N.A.**	4.2	5.3
Q-Sepharose Column Chromatography	N.T.†	2.3	1.1	1.4	<0.9‡
Lyophilization	N.T.†	N.T.†	N.T.†	N.T.†	1.9
Cumulative Total, log_{10}	**10.3**	**6.1**	**5.4**	**5.6**	**7.2**

* Solvent/Detergent treatment inactivates only lipid enveloped viruses. PPV and HAV are non-lipid enveloped viruses.
** Not Applicable for lipid enveloped viruses due to the presence of solvent/detergent in the starting material.
† Not Tested.
‡ Value not included in cumulative total.

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 three to nine months of evaluation.

A study of 25 patients treated with **HEMOFIL** M AHF, and monitored for three to six 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, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified, 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 uses, the dosage should be controlled by frequent laboratory determinations of circulating AHF.

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 AHF.

Warnings

HEMOFIL M, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified, is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. 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 virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. Because this product 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. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Baxter Healthcare Corporation, Hyland Immuno at 1-800-423-2862 (in the U.S.). The physician should discuss the risks and benefits of this product with the patient.

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. 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 three to nine months.

Precautions

General

Certain components used in the packaging of this product contain natural rubber latex.

Identification of the clotting defect as a Factor VIII deficiency is essential before the administration of HEMOFIL M, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified, is initiated.

No benefit may be expected from this product in treating other deficiencies.

The processing of **HEMOFIL** M, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified significantly reduces the presence of blood group specific antibodies in the final product.

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 0.1 ng/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 **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.

Information for Patients

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. Symptoms of parvovirus B19 infection include fever, drowsiness, chills, and runny nose followed about 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 physician if such symptoms appear.

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 Antihemophilic Factor (Human) 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 AHF activity expressed in IU per bottle. This potency assignment is referenced to the World Health Organization International Standard.

The high purity of **HEMOFIL** M AHF has been thought to influence the difficulty of producing an accurate potency measurement. Experiments have shown that to achieve accurate activity levels, such a potency assay should be conducted using plastic test tubes and pipets as well as substrate containing normal levels of von Willebrand's Factor.

The expected *in vivo* peak AHF level, expressed as IU/dL of plasma or % (percent) of normal, can be calculated by multiplying the dose administered per kg body weight (IU/kg) by two. This calculation is based on the clinical finding by Abildgaard, *et al*,[4] which is supported by data from the collaborative study of *in vivo* recovery and survival with 15 different lots of **HEMOFIL** M AHF on 56 hemophiliacs that demonstrated a mean peak recovery point above the mean pre-infusion baseline of about 2.0 IU/dL per infused IU/kg body weight.[5]

Example:

(1) A dose of 1750 IU AHF administered to a 70 kg patient, i.e. 25 IU/kg (1750/70), should be expected to cause a peak post-infusion AHF increase of 25 x 2 = 50 IU/dL (50% of normal).

(2) A peak level of 70% is required in a 40 kg child. In this situation the dose would be 70/2 x 40 = 1400 IU.

Recommended Dosage Schedule
Physician supervision of the dosage is required. The following dosage schedule may be used as a guide.

HEMORRHAGE		
Degree of hemorrhage	**Required peak post-infusion AHF activity in the blood (as % of normal or IU/dL plasma)**	**Frequency of infusion**
Early hemarthrosis or muscle or oral bleed	20-40	Begin infusion every 12 to 24 hours for one-three days until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive hemarthrosis, muscle bleed, or hematoma	30-60	Repeat infusion every 12 to 24 hours for usually three days or more until pain and disability are resolved.
Life threatening bleeds such as head injury, throat bleed, severe abdominal pain	60-100	Repeat infusion every 18 to 24 hours until threat is resolved.
SURGERY		
Type of operation		
Minor surgery, including tooth extraction	60-80	A single infusion plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases.
Major surgery	80-100 (pre- and post-operative)	Repeat infusion every 8 to 24 hours depending on state of healing.

The careful control of the substitution therapy is especially important in cases of major surgery or life threatening hemorrhages.

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

Other dosage regimens have been proposed such as that of Schimpf, *et al,* which describes continuous maintenance therapy.[6]

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, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified, 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 a patient is to receive more than one bottle of **HEMOFIL** M AHF, 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 only.

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.

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 AHF can be stored under refrigeration [2° - 8°C (36° - 46°F)] or at room temperature, not to exceed 30°C (86°F), until expiration date noted on the package. 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: 1. Disruption of lipid enveloped viruses by tri(n-butyl)phosphate detergent combinations. **Transfusion 25**:516-522, 1985
2. Prince AM, Horowitz B, Brotman B: Sterilisation of hepatitis and HTLV-III viruses by exposure to tri(n-butyl) phosphate and sodium cholate. **Lancet 1**:706-710, 1986
3. Kessler CM: An Introduction to Factor VIII Inhibitors: The Detection and Quantitation. **Am J Med 91 (Suppl 5A)**:1S-5S, 1991
4. Abildgaard CF, Simone JV, Corrigan JJ, *et al*: Treatment of hemophilia with glycine-precipitated Factor VIII. **New Eng J Med 275**:471-475, 1966
5. Addiego, Jr. JE, Gomperts E, Liu S. *et al*: Treatment of hemophilia A with a highly purified Factor VIII concentrate prepared by Anti-FVIIIc immunoaffinity chromatography. **Thrombosis and Haemostasis 67**:19-27, 1992
6. Schimpf K, Rothmann P, Zimmermann K: Factor VIII dosis in prophylaxis of hemophilia A; A further controlled study, in **Proc XIth Cong W.F.H.** Kyoto, Japan, Academic Press, 1976, pp 363-366

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