PRODUCT MONOGRAPH

HEMOFIL M

Antihemophilic Factor (Human)

Method M

Monoclonal Purified

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HEMOFIL M

Antihemophilic Factor (Human)
Method M, Monoclonal Purified

ACTION AND CLINICAL PHARMACOLOGY

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 concentration form with a specific activity range of 2 to 15 AHF International Units/mg of total protein.

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.

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.

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.

Use of an organic solvent [tri(n-butyl) phosphate] 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 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 CLINICAL USE

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 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, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified.

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 (See **ACTION AND CLINICAL PHARMACOLOGY**). Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. 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, at 1-800-423-2862. The physician should discuss the risks and benefits of this product with the patient.

Individuals who received 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 **ACTION AND 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 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.

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 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 to be Provided to 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, vomitting 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 inhibitor, additional AHF units will elicit the predicted response.

Use in 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGES

No overdosages has been reported for **HEMOFIL** M, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified.

DOSAGE AND ADMINISTRATION

HEMOFIL M, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified must be administered intravenously.

Each bottle of **HEMOFIL** M AHF is labelled 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 Antihemophilic Factor (Human) (AHF), **HEMOFIL** M, Method M, Monoclonal Purified 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 fifteen different lots of **HEMOFIL** M AHF on forty-three hemophiliacs that demonstrated a mean peak recovery point above the mean preinfusion 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 postinfusion 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 bleed 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 8 to 24 hours until threat is resolved.
Surgery		
Type of operation		
Minor surgery, including tooth extraction	60-80	A single infusion plus oral antifibrinoIytic therapy within one hour is sufficient in approximately 70% of cases.
Major surgery	80-100	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 centre. 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 a 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.

PHARMACEUTICAL INFORMATION

Drug Substance
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.

Composition
HEMOFIL M (AHF) contains a maximum of 12.5 mg/mL Albumin (Human), and per AHF International Unit, 0.07 mg polyethylene glycol (3350), 0.39 mg histidine and 0.1 mg 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. See **ACTION AND CLINICAL PHARMACOLOGY**.

Stability and Storage Recommendations
Store **HEMOFIL** M, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified between 2 to 8°C (36 to 46°F) or room temperature not to exceed 30°C. Please note the expiration date on the package. Avoid freezing to prevent damage to the diluent bottle.

Reconstituted Solutions
HEMOFIL M AHF is supplied as a nonpyrogenic, dried concentration of AHF requiring dilution with 10 mL of Sterile Water for Injection, USP, prior to administration. For concentration of the resulting product, see **Composition**. Do not refrigerate after reconstitution. **HEMOFIL** M, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified, should be administered not more than three hours after reconstitution.

AVAILABILITY OF DOSAGE FORMS
HEMOFIL M AHF, Antihemophilic Factor (Human), is available as single dose bottles. Each bottle is labelled 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.

PHARMACOLOGY

Animal

The role of the Factor VIII complex in hemostasis and blood coagulation has been extensively studied. It is now generally accepted that plasma Factor VIII is a complex of two components that have distinct functions, biochemical and immunological properties, and genetic control. One component of this Factor VIII Complex has antihemophilic factor (AHF) procoagulant activity. The other component, Factor VIII-related protein or von Willebrand factor, interacts with platelets in a manner that promotes primary hemostasis.

Since the efficacy of AHF in correcting coagulation defects of patients with Hemophilic A has been established, only one study of the primary therapeutic activity of AHF prepared by monoclonal antibody purification was performed.

HEMOFIL M AHF is a stable, dried preparation of concentrated Factor VIII prepared from fresh normal human plasma. Its administration can temporarily correct the coagulation defects of patients with Hemophilia A. Under current manufacturing procedures, AHF may contain relatively small amounts of various impurities (e.g. fibrinogen and other proteins). An innovative manufacturing process, monoclonal antibody purification, was developed at Hyland Therapeutics. By using this method, a highly purified Factor VIII (AHF) product with a reduced risk of viral contamination can be manufactured. Since the new process may have altered the biological characteristics of AHF, an assessment of the potential toxicological and pharmacological effects of Factor VIII, AHF monoclonal antibody purified was warranted.

Mouse monoclonal IgG is used in the production and purified of monoclonal antibody AHF.

The efficacy of Antihemophilic Factor (Human), Method M, was compared with that of **HEMOFIL** T (heat-treated). A Cuticle Bleeding Time Test was performed using a Hemophilia A canine model. Bleeding time was determined in 17 normal dogs (5.3 ± 3.6 minutes). Bleeding time was then determined in a hemophiliac dog (30.0 minutes). Two doses (30 Units/kg and 70 Units/kg) of AHF prepared by both methods of manufacture were administered intravenously to the dog at different times. The administration of AHF by both methods of manufacture resulted in a rise in FVIII:C concentration and a decrease in activated partial thromboplastin time and cuticle bleeding time. Bleeding time was 13.2 minutes after administration of **HEMOFIL** T (heat-treated) and 4.5 minutes after AHF prepared by Method M when a dose of 30 Units/kg was administered. When a dose of 70 Units/kg was tested, bleeding time was 4.5 minutes with **HEMOFIL** T and 3.6 minutes with AHF prepared by Method M.

Human

In a pharmacokinetic study performed in 43 patients infused with a nominal dose of 50 IU/kg **HEMOFIL** M, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal

Purified, the half-life was determined to be 14.6 h. The mean recovery was 103.6%, providing approximately a 2% increase in FVIII activity per unit of FVIII/kg infused.[5]

The efficacy and safety of **HEMOFIL** M AHF, in the treatment of Hemophilia A was assessed in 5 hemophiliac patients undergoing elective surgical procedures. Four of the patients had classical Hemophilia A and the fifth patient was a documented female carrier with low plasma FVIII levels. The actual surgical procedures ranged from minor, requiring only local anesthesia to major, which included a cholecystectomy and a bilateral knee replacement. In all cases, hemostasis was maintained. One patient did require a significant amount of AHF to maintain acceptable post-operative FVIII levels. This patient had required 1500 to 2000 U FVIII concentrate prophylactically 3 times a week prior to the surgery and demonstrated a substantial plasma FVIII recovery upon adjusting the dosage regimen. This was therefore considered to be within the normal requirements for this patient by the treating investigator. The two patients who underwent major surgical procedures remained on prophylactic **HEMOFIL** M until they returned to normal physical activity. No clinically significant adverse reactions were noted in any of the patients. The only reaction noted was an "almond taste" which has been frequently reported for plasma-derived FVIII concentrates as "factor taste".

TOXICOLOGY

Animal

The acute intravenous toxicity of **HEMOFIL** M AHF in Sprague-Dawley rats was assessed. **HEMOFIL** M AHF was administered at a rate of 2 mL/min to 23 male and 27 female rats, weighing 173 to 245 grams, aged approximately 8 to 11 weeks at the initiation of the study. The rats were randomly assigned to one of four treatment groups:

- The first group (control) received 0.9% NaCl.
- The second group received the reference product (**HEMOFIL** T – heat-treated product) at a dose of 200 Units/kg.
- The third group received **HEMOFIL** M AHF, at a dose of 100 Units/kg.
- The fourth group received **HEMOFIL** M AHF, at a dose of 200 Units/kg.

Signs of toxicity were recorded within 60 minutes of treatment, at approximately 1 to 3 hours after treatment and daily during a 14 day observation period. Toxicity was assessed on the basis of survival, signs of toxicity, body weight gain, ophthalmic examinations, urinalysis profiles, hematology and clinical chemistry profiles, and gross and microscopic changes. No apparent toxicological manifestations were elicited following acute administration of **HEMOFIL** M AHF.

Studies of subacute, chronic or reproductive toxicity were not considered feasible for **HEMOFIL** M AHF since, as a product containing human proteins, it would elicit hypersensitivity reactions in non-human species resulting in immunoneutralization of potential toxicants. Such reactions would make it invalid to conduct the long-term, repeated-dose studies needed to evaluate these aspects of toxicity. Studies of the oncogenic/carcinogenic potential of **HEMOFIL** M AHF were not considered feasible for the reasons cited above for subacute/chronic/reproductive studies. The absence of

reproductive toxicity studies makes it necessary to include a standard warning statement in the Product Monograph (Category C).

AHF isolation by Method M involves an anti-FVIII immunoaffinity chromatography step. The anti-FVIIIc immunoaffinity resin consists of a highly purified mouse monoclonal antibody which has been immobilized by covalent attachment to cyanogen bromide activated agarose (Sepharose CL-2B).

Although the mouse IgG is covalently attached to the agarose, there is a small percentage of antibody that "leaches" when the immunoaffinity step is performed. This antibody can be detected at low levels in the immunoaffinity column eluate containing the highly purified FVIIIc.

An ion exchange step is also performed in the method M process to reduce the amount of contaminating mouse monoclonal antibody associated with the purified FVIIIc. Substantial separation of the mouse monoclonal antibody occurs at this ion exchange step.

The amount of mouse monoclonal antibody in the final container has been below the level of assay sensitivity, i.e., below 1.0 ng of mouse IgG per mL of reconstitute AHF, or approximately 0.01 ng/AHF unit every lot of AHF produced.

Presently, the highest dose at which AHF is used therapeutically is approximately 200 Units/kg body weight per day for the immunosuppression of "inhibitors". At this dose, a patient receiving **HEMOFIL** M AHF would receive less than 2 ng of mouse monoclonal antibody per kilogram body weight per day.

Despite the very low level of patient exposure to mouse monoclonal antibody, there is the potential risk of an adverse immunological reaction. Experiments were performed to assess this risk. Guinea pigs were chosen because they were considered to be the most sensitive animal model for detecting an immunological reaction.

Three studies were conducted. In the induction phase of each study monoclonal IgG was administered IV to female Hartley albino guinea pigs in volume of 0.1 mL per animal for 14 consecutive days. In the first study, 39 guinea pigs were used. In the second study, 40 guinea pigs were used, weighing between 330 and 448 g. In the third study, 48 guinea pigs were used, weighing between 345 and 450 g. In all studies they were divided into 4 treatment groups. One negative control group was included in the first and second studies, while two negative control groups were included in the third study. During the 14 day induction phase of each study, the animals in the 4 treatment groups received 0.01, 0.10, 1.0 and 10.0 micrograms of mouse mAb.

In the first study, all animals were bled after the induction phase. Serum antibody (IgG) titers were determined by the ELISA procedure. In the second and third studies, the animals were challenged one week after the last intravenous injection (on day 21).

The results of the first study indicated that 13 to 15 animals receiving daily IV dosages of less than 1.0 microgram of mAb did not appear to generate significant levels of

circulating antibody. The results of the third study tended to support the first study. Guinea pigs receiving dosages of 1.0 and 10.0 micrograms of mAb were sensitized as determined by the mean score of erythema/eschar reactions, whereas daily dosages of 100 ng per animal or lower were nonsensitizing. The results of the second study indicate that only the guinea pigs receiving only the highest dosages of 10.0 micrograms of mAb were sensitized.

Human

The only serious adverse reaction observed in animal studies was the sensitization of guinea pigs to mouse monoclonal IgG. Extrapolation of experimental results from an animal model to humans must always be approached with caution. However. the sensitization potential study in guinea pigs is considered to be a reasonable means of evaluating the potential in humans. The sensitization study demonstrated that mouse IgG. used in the preparation of **HEMOFIL** M AHF, did not elicit hypersensitivity reactions in guinea pigs when administered IV at dosages of up to 100 ng/animal for 14 consecutive days. Only at dosages of 1 microgram/animal (which corresponds to approximately 2.5 micrograms per kilogram body weigh) or greater was mouse monoclonal IgG shown to have a sensitization potential in guinea pigs. This, in humans, dosages of less than 2.5 micrograms per kilogram body weight would not be expected to be associated with sensitization and the development of circulating anti-mouse monoclonal antibody titers.

As mentioned above, the highest dose at which AHF is used therapeutically is approximately 200 Units/kg per day for the immunosuppression of "inhibitors". A patient receiving this dose of **HEMOFIL** M AHF would receive less than 0.002 micrograms of mouse monoclonal antibody per kilogram body weight per day. This amount of monoclonal antibody is approximately 3 orders of magnitude lower than dosages that required to sensitize guinea pigs and 2 orders of magnitude lower than dosages that did not sensitize guinea pigs. Therefore, the sensitization potential of mouse monoclonal antibody present in **HEMOFIL** M AHF would be relatively low in humans.

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