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Hemofil

Antihaemophilic Factor (Human) Method Four, Dried

The potency of each lot of this product is given on the container and package labels. See instructions given under **Administration** for potency-related administration instructions.

DESCRIPTION

HEMOFIL Antihaemophilic Factor (Human), Method Four* is a stable, dried preparation of antihaemophilic factor (Factor VIII, AHF, AHG) in concentrated form. It is prepared from fresh, normal human plasma and contains approximately 3 % w/v dextrose in the reconstituted material as a solubilising agent. The product also contains a trace amount of heparin, 1.0 unit (0.010 mg) or less per ml of reconstituted material, as a stabiliser. Concentrations of heparin many times greater than this have been shown[1] to have no demonstrable effect after infusion of the volumes encountered in the use of this product. HEMOFIL Antihaemophilic Factor (Human) offers many advantages, the most significant of which are:

1. Because it contains higher AHF potency than cryoprecipitate preparations with relatively small amounts of fibrinogen and other proteins, adequate AHF can be furnished without excessively overloading the circulatory system.
2. It may be administered either by intravenous drip infusion or by direct syringe injection.
3. Each lot is assayed and labelled for its AHF content. This permits estimation of dose needed and prediction of effect when compared to the variability of AHF content in cryoprecipitate preparations.
4. Because of the predictable effect, therapy may be managed without repeated determinations of AHF levels. This is especially important when the patient is very young, when the patient's veins are poor or when laboratory service is not readily available.
5. AHF is very stable in the dry form.

ACTION

Antihaemophilic factor (AHF) is a protein found in normal plasma which is necessary for clot formation. The administration of HEMOFIL Antihaemophilic Factor (Human) provides an increase in plasma levels of AHF and can temporarily correct the coagulation defect of patients with haemophilia A (classical haemophilia).

INDICATIONS

The use of HEMOFIL Antihaemophilic Factor (Human) is indicated in haemophilia A (classical haemophilia) for the prevention and control of haemorrhagic episodes.

The concentrate can be of significant therapeutic value in patients with acquired Factor VIII inhibitors.[2] However, in such uses the dosage should be controlled by frequent laboratory determinations of circulating Factor VIII.

This product is not known to contain clotting factors other than AHF; therefore, no benefit may be expected from its use in treating other deficiencies. **Identification of the deficiency as one of Factor VIII is imperative before administration of this highly purified antihaemophilic factor.**

Antihaemophilic Factor (Human) is not indicated in von Willebrand's disease.

CONTRAINDICATIONS

There are no known contraindications to the use of this concentrate.

WARNINGS

This concentrate is prepared from large pools of fresh human plasma. Such plasma may contain the causative agent of viral hepatitis. However, each unit of the plasma used in the manufacture of this product has been found to be nonreactive for hepatitis B surface antigen (HB_sAg) by radioimmunossay. The concentrate has not been subjected to any treatment known to diminish the risk of hepatitis transmission since such treatments greatly increase the loss of AHF activity during preparation. The concentrate should, therefore, be used when the need for its expected effect outweighs the hepatitis risk associated with its use.

This lot, after reconstitution as for use, has been found nonreactive for hepatitis B surface antigen (HB_sAg) using a solid phase radioimmunoassay technique licensed by the U.S. Bureau of Biologics. The significance of a nonreactive test result with concentrated antihaemophilic factor has not been established. Therefore, the product should continue to be considered to carry a risk with respect to hepatitis.

PRECAUTIONS

This Antihaemophilic Factor (Human) preparation contains blood group isoagglutinins (anti-A and anti-B). When large or frequently repeated doses are needed, as when inhibitors are present or when pre- and post-surgical care is involved, patients of blood groups A, B and AB should be monitored for signs of intravascular haemolysis and decreasing haematocrit values. Haemolytic anaemia, when present, may be corrected by the administration of compatible Group O Human Red Blood Cells.

Since HEMOFIL contains small residual amounts of fibrinogen which tend to cause the ground surfaces of glass to stick, plastic (disposable) syringes should be used when administration by syringe is desired.

ADVERSE REACTIONS

Allergic reactions may be encountered from the use of AHF concentrate preparations.

The risk of hepatitis is present with the administration of AHF concentrate preparations (see discussion under WARNINGS).

DOSAGE AND ADMINISTRATION

Each bottle of HEMOFIL Antihaemophilic Factor (Human), Method Four is labelled with the number of International Units of AHF activity which it contains, each Unit being defined as the activity present in 1 ml of normal pooled human plasma less than 1 hour old (100 % AHF level).

Dosage

Abildgaard *et al*[3] reported that infusion of 1 unit of AHF per kg body weight consistently produces an increase of 2 % (of normal), while Shanbrom and Thelin[4] found that 3.8 to 4.0 units per kg produce an increase of 10 % (of normal) in AHF level. (The former authors worked with boys 8 months to 14 years of age, while the latter worked primarily with adults). The following formulae can therefore be used to calculate, approximately, the expected response from a given dose or the dose required for a given effect:

1. Units required = body weight (in kg) x 0.4 x desired AHF increase (in % of normal)

   Example: 70 x 0.4 x 50 = 1400 units

or

2. Expected AHF increase (in % of normal) =

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

Example: $\frac{1400}{70 \times 0.4} = 50\ \%$

The data of Abildgaard, *et al*, and more recently that of Biggs, *et al*[5], would call for a factor of 0.5 instead of 0.4 in the above formulae.

The amount of AHF that a haemophiliac requires for normal haemostasis varies with circumstances and with the patient. The amount of factor to be supplied will depend on the degree of deficiency and on the AHF level desired.

Kasper has found that minor haemorrhagic episodes will generally subside with a single infusion if a level of 30 % or more is attained. For more serious haemorrhages, a Factor VIII level of 35 to 50 % of normal should be obtained for optimum clot formation. In surgery, Kasper recommends that the first dose of Factor VIII, to achieve a level of 80 to 100 %, be given an hour before the procedure. A second dose of Factor VIII half the size of the priming dose should be given about 5 hours after the priming dose. If several units of blood were lost during the operation, a third dose of concentrate should be given when the patient returns from the theatre. The Factor VIII level should be maintained at a daily minimum of at least 30 % for a healing period of 10 to 14 days[6].

The above dosage formulae are presented as a reference and a guideline. Other dosage regimes have been proposed and are being used by other clinicians.

Exact dosage determinations should be made based on the medical judgement of the physician regarding circumstances, condition of patient, degree of deficiency and the desired level of Factor VIII to be achieved.

The half-life of AHF administered to haemophiliacs has been variously estimated at 8 to 24 hours.[7–11] In the severe haemophiliac, the half-life of the first dose of AHF in any form appears to be at the lower end of the range, but for subsequent doses it may be safely estimated as at least 12 to 15 hours in the absence of inhibitors and "active bleeding".

Although dosage can be estimated by these calculations, 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 level 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 AHF inhibitor can be demonstrated and quantitated in terms of AHF units neutralised by each ml of plasma or by the total estimated plasma volume. After sufficient dosage to neutralise inhibitor, additional dosage produces predicted clinical response. It should be noted that when inhibitor is present, measurement of Lee-White clotting time may be a better index of adequacy of dosage than measurement of circulating AHF.

Reconstitution

HEMOFIL Antihaemophilic Factor (Human), Method Four contains approximately 3 % w/v dextrose in the reconstituted product in order to improve its solubility characteristics.

The solution should be administered promptly after reconstitution. The reconstituted material should not be refrigerated as irreversible precipitation of active material may occur.

1. If refrigerated, warm diluent (water) and concentrate in unopened bottles to room temperature (20° to 30°C) — keep at this temperature during reconstitution.

CAUTION: If a water bath is used for warming to 20° to 30°C, do not allow the water to contact any portion of the seals or stoppers.

2. Remove caps from HEMOFIL and diluent bottles to expose central portions of rubber stoppers.
3. Cleanse stoppers with antiseptic solution.

When reconstituting with a double-ended needle:

4. Remove protective covering from one end of double-ended needle, using care not to touch exposed end. Insert exposed needle through **diluent** stopper.
5. Remove protective covering from other end of double-ended needle, using aseptic precautions as above. Invert diluent bottle over the upright HEMOFIL bottle, then **rapidly** insert free end of the needle through the HEMOFIL bottle stopper at its centre. Vacuum in HEMOFIL bottle will draw in diluent.

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6. Disconnect the two bottles by removing needle from HEMOFIL bottle stopper. **Shake vigorously for 5 seconds,** then agitate or rotate HEMOFIL bottle until all concentrate is dissolved. AHF activity is not diminished by holding the material at 20° to 30°C for as long as 1 hour. **Be sure that concentrate is completely dissolved; otherwise, active material will be removed by the filter.** The material is now ready for administration (see **Administration**).

When reconstituting with a syringe:

4. Without touching exposed needle, attach **filter** needle to syringe (use plastic syringe), withdraw entire contents of the diluent (water) bottle into syringe, then inject diluent into bottle of dry concentrate.
5. Withdraw needle from the HEMOFIL bottle stopper, leaving needle on syringe and protect needle from contamination. **Shake vigorously for 5 seconds,** then agitate or rotate HEMOFIL bottle until all concentrate is dissolved. AHF activity is not diminished by holding the material at 20° to 30°C for as long as 1 hour. **Be sure that concentrate is completely dissolved; otherwise, active material will be removed by the filter.** Proceed with administration (see **Administration**).

Administration

HEMOFIL preparations containing 34 or more International Units per ml must be administered at carefully controlled rates, i.e., **a maximum infusion rate of 2 ml per minute.** Accordingly, the infusion of a 30 ml total volume containing 34 or more International Units per ml must be evenly regulated over a period of 15 or more minutes. AHF preparations containing less than 34 International Units per ml can be given rapidly, either by intravenous drip infusion or direct syringe injection, at a rate of 10 to 20 ml over a 3 minute period, with no significant reactions.

A. Intravenous Drip Infusion

1. After reconstituting HEMOFIL as directed under **"Reconstitution",** follow directions accompanying the administration set being used.
   NOTE: Ensure administration set used contains an adequate filter.
2. Discard administration set after use. Also discard any reconstituted concentrate not used at one time.

B. Intravenous Syringe Injection

As a precautionary measure, the physician should determine the pulse rate before and during administration of the AHF concentrate. Should a significant increase of pulse rate occur, reduce the rate of administration or discontinue. Preparations containing less than 34 International Units per ml may be injected at a rate of 10 to 20 ml over a 3 minute period. Preparations containing 34 or more International Units per ml may only be injected at a maximum rate of 2 ml per minute.

1. After reconstituting HEMOFIL as directed under **"Reconstitution",** re-insert **filter** needle (on syringe) through the bottle stopper.
2. Inject air and withdraw the reconstituted AHF into the syringe.
3. Remove and discard the **filter** needle from the syringe; attach a suitable needle and inject intravenously.
4. If the same patient is to receive more than one bottle of concentrate, the contents of two bottles may be drawn into the same syringe through **filter** needles before attaching the vein needle. For additional bottles, the same syringe may be refilled through **filter** needles; this practice lessens the loss of concentrate.

STORAGE

HEMOFIL Antihaemophilic Factor (Human), Method Four should be stored under ordinary refrigeration (2° to 8°C). It may be stored for no longer than 6 months within the dating period at room temperature, not exceeding 25°C. Freezing should be avoided as damage to the diluent bottle may occur.

HOW SUPPLIED

HEMOFIL Antihaemophilic Factor (Human), Method Four is supplied in vials containing 10 ml or 30 ml of dried concentrate, together with a suitable volume of Water for Injections Ph. Eur.

The potency in International Units (I.U.) of AHF activity, as determined for each lot, is stated on the label of each bottle.

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