HUMANATE is prepared from human venous plasma. Each unit of donor plasma has been tested for Hepatitis B Surface Antigen by a radioimmunoassay technique and found non-reactive. However, the test does not necessarily preclude the presence of Hepatitis Virus.

Description

HUMANATE, antihaemophilic factor (human) is a highly purified and stable, freeze dried concentrate of Factor VIII (AHF, AHG) intended for use in the treatment of classical haemophilia (haemophilia A).

It is purified from the cold insoluble fraction of pooled fresh frozen plasma by the method first described by Hershgold, Pool and Pierpont-Hegan[1] subsequently modified and refined.

The product is between 40 and 170 times purified, when compared with whole plasma and contains minimal quantities of fibrinogen.

HUMANATE is thus a highly potent source of Factor VIII activity, containing between 25 and 30 times as much Factor VIII as an equal volume of fresh frozen plasma.

The level of Factor VIII in the circulation can be raised significantly by the administration of relatively small volumes of HUMANATE. For example, 500 international units (the amount normally present in 500 ml of fresh frozen plasma) can be given in an injection volume of only 20 ml, with a total protein content of around 0.5 gm.

HUMANATE offers many advantages over whole blood, plasma, cryoprecipitate and less potent concentrates. The most significant of these are -

1. High potency. The non-Factor VIII protein load is extremely low. Adequate Factor VIII can be injected, with relatively small amounts of contaminating fibrinogen and other proteins, in a relatively small dose volume.

This is of especial value when it is necessary to maintain high circulating levels of Factor VIII for prolonged periods and in the treatment of inhibitor patients.

2. Stability. HUMANATE is presented as a freeze dried powder. Factor VIII activity is not subject to decay, provided the recommended storage instructions are followed.

3. Solubility. HUMANATE dissolves rapidly, without the excessive shaking and foaming which can inactivate Factor VIII.

4. Rapid injection. The high purity enables HUMANATE to be administered by direct syringe injection, without significant side effects, thus making it ideal for home treatment.

5. Side effects. HUMANATE contains no thrombin or thromboplastin-like activity, no depressor activity and low levels of anti-A and anti-B isoagglutinins. No heparin is present and it is not necessary to add this before use.

6. Dose volume. The injection volume required to achieve and maintain haemostasis is minimal. HUMANATE is presented as nominal vial sizes of 250 International Units in 10 ml, 500 in 20 ml and 1000 in 40 ml.

Action

Factor VIII (Human) is a plasma protein which is an essential component of the intrinsic pathway for the conversion of prothrombin to thrombin. It thus corrects the coagulation defect present in patients with haemophilia A.

Indications

HUMANATE is indicated for the temporary replacement of demonstrated deficiencies of Factor VIII. It can be used to correct or prevent bleeding episodes and for Factor VIII replacement prior to emergency or elective surgery.

Precautions

1. Deficiency of Factor VIII should be established prior to therapy with HUMANATE. No benefit will arise from its administration for other causes of haemorrhage.

2. HUMANATE should be administered immediately after reconstitution. Do not refrigerate after reconstitution. Discard any unused material.

3. HUMANATE must be administered intravenously.

4. The enclosed sterile filter needle must be used prior to administering the product. See directions below.

5. HUMANATE contains levels of blood group isoagglutinins which are of no defined significance in many cases. However, when large or frequently repeated doses are necessary in patients with blood groups A, B or AB, the possibility of intravascular haemolysis should be monitored.

Adverse Reactions

No severe adverse reactions have been reported during clinical trials and subsequent usage of HUMANATE. Mild allergic reactions may result.

Where intravascular haemolysis occurs, following large or frequently repeated doses, administration of serologically compatible red blood cells should be considered[2]. The administration of type-specific cryoprecipitate is also recommended[3].

Dosage

The antihaemophilic activity contained in each bottle of HUMANATE is clearly indicated on the label in International Units. One unit is defined as the activity contained in 1 ml of average normal plasma.

The dose of HUMANATE required for haemostasis control must be determined for each individual patient. The required dose is dependent upon:-

1. the weight of the patient
2. the severity of the deficiency in the patients factor VIII level
3. the type of haemorrhage
4. the presence of inhibitors
5. the desired factor VIII level.

It has been reported (Abildgaard et al[4]) that, in haemophilic children, there is a linear dose response, with an approximate 2 per cent rise in Factor VIII level for every unit of Factor VIII infused per kilo of body weight.

The dosage regime below has generally been found satisfactory.

1. Joint Haemorrhages

Without aspiration, 10 units/kg at 8 to 12 hour intervals, for a period of time dependent on the severity of the bleed and the response, as measured by pain relief, reduction in swelling and improved joint movement.

Early joint bleeds, when treated promptly, will respond to a single dose of 10 units/kg[5].

If the joint is aspirated, 10 units/kg should be given immediately prior to the aspiration, followed by a similar dose after 6-8 hours, repeated as necessary.

A fully developed haemarthrosis can be treated with a dose calculated to achieve a Factor VIII level of 50 per cent, say 25 units/kg[5].

2. Muscle Haemorrhages

(a) Minor haemorrhages in the non-vital areas – 10 units/kg, 8 to 12 hourly, until pain and swelling are relieved.

(b) Massive haemorrhages in non-vital areas – a similar dose, infused at 8 to 12 hour intervals for two or more days, subject to pain relief, improvement of the haemorrhage

if this has dropped) and relief of other symptoms associated with the haemorrhage.

b) Haemorrhages located near vital organs – initially, 20 units/kg, followed by 10 units/kg every 8 hours for 2 days. 5 units/kg every 8 hours for a further 2 days.

2. Overt bleeding
Initially, 20 units/kg, then 10 units/kg every 8 hours for the first 24, then every 12 for 3 to 4 days, or as necessary.

4. Massive wounds
Administer HUMANATE until the bleeding is arrested, followed by 20 units/kg every 8 hours. Dosage should be designed to maintain a minimum level of 40 per cent Factor VIII.

5. Surgery [7, 8, 9]
The minimum Factor VIII level required for surgery is 40 per cent. Higher figures are desirable for surgery in the central nervous system.

30 to 40 units/kg should be given before surgery commences, then afterwards, 20 units/kg every 8 hours. Laboratory control should be constant and the dose increased if the patient's level falls below 30 per cent.

The post administration level should be 50 per cent and it is suggested[8] that between 30 and 40 per cent of normal should be maintained for at least 10 post-operative days.

The formula below can be used to calculate the dose required or the likely effect from a given dose:

Expected Factor VIII increase (in % of normal levels) = units administered divided by body weight in kg.

Without direct laboratory evidence, it is sometimes dangerous to assume a certain response and frequent monitoring of Factor VIII levels is desirable.

6. Prophylaxis
There is extensive published experience of prophylactic treatment of haemophilia A.[10, 11, 12] Keeper et al[11] suggest 250 units per day for patients of 50 kg or less and 500 units for those above 50kg administered in the morning. Where bleeding episodes continue, the dose is increased until a satisfactory protection level is observed.

7. Inhibitor patients
When inhibitors to Factor VIII are present, dosage requirements are most variable. The presence of an inhibitor can be established and quantified by laboratory procedures, but the dosage is often best determined by clinical response.

8. General
Clinical effect is the most important indicator of effectiveness of treatment. Factor VIII doses higher than calculated may be necessary.

Preconstitution & Administration
1. Warm unopened vials of diluent and HUMANATE to room temperature (max. 37°C).

2. Remove plastic seals from both bottles and clean the exposed central portion of each rubber stopper with a suitable antiseptic immediately prior to piercing.

3. Withdraw the appropriate quantity of diluent (Water for Injection USP) with a sterile needle and syringe and transfer to the bottle of HUMANATE.
Add slowly to avoid frothing.

4. Withdraw needle and gently shake vial until powder is completely dissolved. Solution is usually complete within 5 minutes.

5. After the powder is completely dissolved, withdraw the solution into the syringe through the enclosed filter needle. Replace this needle with an appropriate sterile injection needle and inject intravenously.

Storage
HUMANATE is stable for 2 years from the date of manufacture, if stored between 2 and 8°C, except that it can be kept at room temperature for up to a maximum of 6 months during this period.

Freezing must be avoided, to prevent breakage of the diluent vial.

Reconstituted HUMANATE must not be refrigerated and should be used immediately.

Presentation
HUMANATE is supplied in single dose containers with a suitable volume of Sterile Water for Injection USP and a sterile filter needle in each pack.

The cartons and labels indicate the total Factor VIII activity and total protein in each container. Potency does, of course, vary from batch to batch. Three pack sizes are available.

	Order code
Nominal 250 units	HE 01
Nominal 500 units	HE 02
Nominal 1000 units	HE 03

Warranty
No warranty, express or implied, including any warranty of merchantability or fitness is made and the user of this product must accept the terms hereof.

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Sanwood Laboratories Limited
Church House East Street
Bingham Nottingham England

Telephone Bingham (0949) 39665.
Telex 377139

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