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ANTIHAEMOPHILIC FACTOR
(HUMAN) dried
Profilate® Heat-Treated

DESCRIPTION

Antihaemophilic Factor (Human), Profilate®, Heat-Treated is a stable freeze dried concentrate of Factor VIII (AHF, AHG) prepared from pooled plasma by cryoprecipitation of the active factor and its subsequent purification and concentration by chemical means. The potency (Antihaemophilic Factor) is expressed on the bottle label in International Units (I.U.). Profilate® Heat-Treated is a sterile preparation intended for intravenous administration. Each vial is a single dose container.

This product is prepared from units of human plasma which have been tested and found nonreactive for hepatitis B surface antigen (HBsAg) by an FDA required test. However, methods presently available are not sensitive enough to detect all units of potentially infectious plasma, and the risk of transmitting hepatitis is still present.

The process used in the manufacture of Profilate® Heat-Treated includes a step designed to reduce the risk of transmission of hepatitis, Acquired Immune Deficiency Syndrome (AIDS), and infection by other viruses. However, no method has been shown to be totally effective in removing hepatitis, AIDS, or other viral infectivity from Antihaemophilic Factor (Human).

CLINICAL PHARMACOLOGY

Antihaemophilic Factor (Factor VIII) is a constituent of normal plasma required for clotting. The administration of Antihaemophilic Factor (Human), Profilate® Heat-Treated temporarily increases the plasma levels of this clotting factor, thus minimizing the hazards of haemorrhage.[1,2]. Following administration, the half-life of Factor VIII is approximately 8 to 15 hours.

The effectiveness of the heat-treatment step was assessed by in-vitro inactivation studies using live viruses added to Antihaemophilic Factor (Human) Profilate® Heat-Treated. A newly recognized retrovirus has been implicated as a possible causative agent of Acquired Immune Deficiency Syndrome (AIDS). This virus has been given several names, including human T-lymphotropic virus type III (HTLV-III), lymphadenopathy-associated virus (LAV), and AIDS-associated retrovirus (ARV) and has been commonly referred to in the literature as HTLV-III/LAV. The heat-treatment process used in the manufacture of Profilate® Heat-Treated has been shown to inactivate a minimum of 3.25 Logs of HTLV-III/LAV virus when the virus was intentionally added to the product.

The following table shows the total number of logs of each virus inactivated.

VIRUS	LOGS INACTIVATED
HTLV-III/LAV	at least 3.25
Cytomegalovirus (CMV)	>2.0
Sindbis	4.61
Vesicular Stomatitis	5.83

Chimpanzee studies demonstrate that the heat-treatment step is effective in inactivating at least 500 chimpanzee infectious doses (CID) of hepatitis B virus. Neither of two chimpanzees receiving 500 CID of hepatitis B virus contracted hepatitis B six months post inoculation. One of two chimpanzees who received 10,000 CID was free of hepatitis B for at least 12 months.

The chimpanzee study also showed that the process inactivated an undetermined quantity of at least one type of non-A, non-B hepatitis present in the Antihaemophilic Factor (Human).

INDICATIONS AND USAGE

Antihaemophilic Factor (Human), Profilate® Heat-Treated is indicated solely for the prevention and control of bleeding in patients with moderate or severe Factor VIII deficiency due to haemophilia A, or acquired Factor VIII deficiency.[3] Antihaemophilic Factor (Human), Profilate® Heat-Treated is not indicated in the management of bleeding in patients with von Willebrand's disease.

CONTRAINDICATIONS

None known.

WARNINGS

Viral hepatitis may be transmitted by this product. Patients with mild deficiencies, who consequently have not received multiple transfusions of blood or blood products, are at greatest risk.[4,7] In this situation, the benefits of Antihaemophilic Factor (Human), Profilate® Heat-Treated administration must be carefully weighed against the risk of viral hepatitis; single donor products should be preferentially utilized whenever feasible.

The causal factors of Acquired Immune Deficiency Syndrome (AIDS) have not been fully defined. However, HTLV-III/LAV virus has been implicated as a possible agent of the disease. It is not presently known if other transmissible agents are

involved. Alpha uses screening procedures to eliminate high risk plasma donors and a heat-treatment step in the manufacturing process to reduce the risk of transmitting AIDS. However, despite the careful selection of donors, it may be possible that the AIDS causative agents may still be present in and be transmitted through this product.

PRECAUTIONS

General: Antihaemophilic Factor (Human), Profilate® Heat-Treated should not be administered at a rate exceeding 10 ml/minute. Rapid administration may result in vasomotor reactions.

Some patients develop inhibitors to Factor VIII. In patients with inhibitors, the response to Antihaemophilic Factor (Human), Profilate® Heat-Treated may be much less than would otherwise be expected and larger doses are often required. The management of patients with inhibitors requires careful monitoring, especially if surgical procedures are indicated.[8,11,12]

Nursing personnel and others who administer this material should exercise appropriate caution in handling because of the risk of exposure to viral hepatitis.

Discard any unused contents. Discard administration equipment after single use. Do not resterilize components.

ADVERSE REACTIONS

Adverse reactions may include urticaria, fever, chills, nausea, vomiting, headache, somnolence or lethargy. Some patients develop reactions of a mild nature following the administration of Antihaemophilic Factor (Human), Profilate® Heat-Treated.[10] Adverse reactions may be on an allergic basis. If a reaction is noted and the patient requires additional Antihaemophilic Factor (Human), Profilate® Heat-Treated, product from a different lot should be administered.

Massive doses have rarely resulted in acute haemolytic anemia, increased bleeding tendency or hyperfibrinogenemia.[5]

Antihaemophilic Factor (Human), Profilate® Heat-Treated contains blood group specific isoagglutinins and when large and/or frequent doses are required in patients of blood group A, B, or AB, the patient should be monitored for signs of intravascular haemolysis and falling Hematocrit. Should this condition occur, thus leading to progressive haemolytic anemia, the administration of serologically compatible type O red blood cells should be considered.

DOSAGE AND ADMINISTRATION

Antihaemophilic Factor (Human), Profilate® Heat-Treated must be administered intravenously within three hours following reconstitution with the diluent supplied. Antihaemophilic Factor (Human), Profilate® Heat-Treated may be administered either by injection (plastic syringe only) or infusion.

After reconstitution, parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Antihaemophilic activity is expressed in International Units (I.U.). One unit approximates the activity in one ml of plasma. The following formula provides a guide for dosage calculations:

$$\text{Number of AHF units required} = \text{Body weight in lbs} \times 20 \times \text{Desired increase in Factor VIII percentage}$$

Example: 110 lbs x 20 x 0.30 = 660 AHF units

$$\text{Number of AHF units required} = \text{Body weight in kg} \times 44 \times \text{Desired increase in Factor VIII percentage}$$

Example: 50 kg x 44 x 0.30 = 660 AHF units

Mild to moderate haemorrhages may usually be treated with a single adminstration sufficient to raise the plasma AHF level to 20 to 30 percent. In the event of more serious haemorrhage the patient's plasma AHF level should be raised to 30 to 50 percent; infusions are generally required at twice daily intervals over several days.[9]

Surgery in patients with Factor VIII deficiency requires that the AHF level be raised to 50 to 80 percent with the level maintained at or above 30 percent for approximately two weeks post-operatively. For dental extractions, the AHF level should be raised to 50 percent immediately prior to the procedure; further Factor VIII may be given if bleeding recurs.[9]

In patients with severe Factor VIII deficiency who experience frequent haemorrhages, Antihaemophilic Factor (Human), Profilate® Heat-Treated is administered prophylactically on a daily or every other day schedule so as to raise the AHF level to approximately 15 percent.[6]

RECONSTITUTION

Use Aseptic Technique

1. Warm diluent and concentrate bottles to at least room temperature (but not above 37°C).

2. Remove plastic flip-off cap from the diluent bottle.

3. Swab the exposed rubber surface with alcohol. Do not leave excess cleaning agent in indentation on stopper.

4. Remove covering from one end of a double ended needle. Insert this exposed end of the needle through the depression in the center of the stopper in the bottle of diluent.

5. Remove plastic flip-off cap from the concentrate bottle. Tap bottle gently to dislodge concentrate from sides of bottle.

6. Swab the exposed rubber surface with alcohol. Do not leave excess cleaning agent in indentation on stopper.

7. Remove plastic cap from the upper end of the double ended needle now seated in the stopper of the diluent bottle. Hold concentrate bottle in one hand, invert the bottle of diluent in the other hand and push the exposed end of the needle through the depression in the center of the stopper, making certain that the diluent is always above the bottle of concentrate. There should be enough vacuum in the bottle to draw in all the diluent.

8. Disconnect the two bottles by removing needle from the concentrate bottle stopper. Shake vigorously for ten seconds, then agitate or rotate concentrate bottle until all concentrate is dissolved. Reconstitution requires approximately five to ten minutes. When the reconstitution procedure is strictly followed a few small particles may occasionally remain. The microaggregate filter will retain particles and the labeled potency will not be reduced.

ADMINISTRATION

By Syringe:

Use Aseptic Technique

1. Peel cover from Alpha Micron Filter package and securely install the syringe into the exposed luer inlet of the filter using a slight clockwise twisting motion.

2. Remove filter from blister-pak cup. If present, remove protective sleeve from the spike end of the filter using a clockwise twisting motion.

3. Pull back plunger to aspirate sufficient air into the syringe to allow reconstituted product to be withdrawn as described in the next step.

4. Insert the spike end of the filter into the reconstituted concentrate bottle. Inject air and aspirate the reconstituted product from the bottle into the syringe.

5. Remove and discard the filter from the syringe and attach syringe to an infusion set, expel air from syringe, perform venipuncture and administer slowly.

6. If the patient is to receive more than one bottle of concentrate, the infusion set will allow this to be performed with a single venipuncture.

7. Discard all administration equipment after use.

ADMINISTRATION

By Administration Set:

Use Aseptic Technique

1. Close clamp on administration set.

2. With bottle upright, insert piercing pin straight through stopper center. Do not twist or angle.

3. Immediately invert bottle to automatically establish proper fluid level in drip chamber (half full).

4. Attach infusion set, open clamp and allow solution to expel air from tubing needle, then close clamp.

5. Perform venipuncture and adjust flow.

6. Discard all administration equipment after use.

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HOW SUPPLIED

Antihaemophilic Factor (Human), Profilate® Heat-Treated is supplied in single dose bottles, with suitable volume of diluent. AHF activity, expressed in International Units (I.U.), is stated on the label of each concentrate bottle.

STORAGE

Antihaemophilic Factor (Human), Profilate® Heat-Treated should be stored at temperatures between 2°-8°C. Do not freeze.

References

1. Properties of Factor VIII (Antihaemophilic Factor) in Progress in Hemostasis and Thrombosis Volume 2, T.H. Spaet, editor, Grune and Stratton Publisher, pp. 99-139, 1974.

2. Ashenhurst, J.B., Langehenning, P.L., and Seeler, R.A. "Early Treatment of Bleeding Episodes with 10u/kg of Factor VIII," Blood 50, p. 181, 1977.

3. Eyster, M.E. "Hemophilia: A Guide for the Primary Care Physician," Postgraduate Medicine, 64, pp. 75-81, 1978.

4. Biggs, R. "Jaundice and Antibodies Directed Against Factors VIII and IX in Patients Treated for Haemophilia or Christmas Disease in the United Kingdom," British Journal of Haemotology 26: 313-29, 1974.

5. Hathaway, W.E., Mahasandana, C. and Clarke, S. "Alteration of Platelet Function after Transfusion in Hemophilia," Abstracts. 14th Annual Meeting, American Society of Hemotology, San Francisco, CA, December 5-7, 1971, p. 58, No. 88.

6. Kasper, C.K., Dietrich, S.L. and Rapaport, S.I. "Hemophilia Prophylaxis with Factor VIII Concentrate," Archives of Internal Medicine 125: 1004-9, June 1970.

7. Kasper, C.K. and Kipnis, S.A. "Hepatitis and Clotting-Factor Concentrates," Journal of the American Medical Association 221: 510, 1972.

8. Kasper, C.K. "Incidence and Course of Inhibitors Among Patients with Classic Hemophilia," Thrombosis et Diatheses Haemorrhagica 30: 263-71, 1973.

9. Kasper, C.K. "Hemophilia and Hemophilioid Disorders," (In) Conn, H.F. (Ed) Current Therapy, 4th ed, Philadelphia, pp. 258-63, Saunders, 1974.

10. Rizza, C.R. and Biggs, R. "Blood Products in the Management of Haemophilia and Christmas Disease," (In) Poller L. (Ed) Recent Advances in Blood Coagulation, Boston, pp. 179-95, Little Brown, 1969.

11. Rizza, C.R. and Biggs, R. "The Treatment of Patients Who Have Factor VIII Antibodies," British Journal of Haematology 24: 65-82, 1973.

12. Roberts, H.R., Knowles, M.R., Jones, T.L. and McMillan, C. "The Use of Factor VIII in the Management of Patients with Factor VIII Inhibitors," (In) Brinkhous, K.M. (Ed) Hemophilia and New Hemorrhagic States, International Symposium, New York, pp. 152-63, University of North Carolina Press, 1970.

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