REVLON HEALTH CARE (UK) LIMITED

**INTER OFFICE MEMORANDUM**

R.B.C. - 5 JUL 1985

Armour Pharmaceutical Company Limited B0000149

BERK Pharmaceuticals Ltd.

TO : Dr. C. Swartz

DATE: 3rd July 1985.

FROM : C.R. Bishop

REF: CRB/BAK

SUBJECT : FACTORATE HEAT TREATED - NEW DATA SHEETS/PACKAGE INSERTS

COPIES TO :

L. Lucas
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R.B. Christie
A. Sheppard
Master
Day
File

We have to reprint our current inserts and Data Sheets and we would be grateful if you could confirm what we can authoratively add regarding viral inactivation of our product at this stage.

It is a requirement of our licensing that we show the heat treating process.

Attached is a copy of the Profilate insert, which does not fulfil the requirements of the licence in that it does not show the heat treating process, but they do have some information on viral inactivation.

Your urgent and valuable assistance would be greatly appreciated.

Regards,

GRO-C

C.R. Bishop.

REV 48

5. Insert tapered spike into reconstituted concentrate bottle perpendicular to stopper. If spike is not held perpendicular it may push stopper into bottle rendering contents unusable.
6. Remove and discard the filter spike from the syringe and attach syringe to an infusion set, expel air from syringe, make venipuncture and administer slowly.
7. If the patient is to receive more than one bottle of concentrate, the infusion set will allow this to be done with a single venipuncture.
8. Discard all administration equipment after use.

**ADMINISTRATION**
**By Infusion Set:**
**USE ASEPTIC TECHNIQUE**

1. Close clamp on administration set.
2. With bottle upright, thrust 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. Make venipuncture and adjust flow.
6. Discard all administration equipment after use.

## HOW SUPPLIED

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

## STORAGE

Antihemophilic Factor (Human), Profilate® Heat-Treated may be stored at temperatures between 2°-8°C for two years. Do not freeze.

**CAUTION:** Federal (U.S.A) law prohibits dispensing without a prescription.

## REFERENCES


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Alpha
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# ANTIHEMOPHILIC FACTOR (HUMAN), dried PROFILATE® HEAT-TREATED

B0000150/1

## DESCRIPTION

Antihemophilic 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 (Antihemophilic 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. Contains dextrose, not more than 4 milligrams per AHF unit, as a solubilizing agent.

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 Antihemophilic Factor (Human).

## CLINICAL PHARMACOLOGY

Antihemophilic Factor (Factor VIII) is a constituent of normal plasma required for clotting. The administration of Antihemophilic Factor (Human), Profilate® Heat-Treated temporarily increases the plasma levels of this clotting factor, thus minimizing the hazards of hemorrhage.[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 Antihemophilic 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 Antihemophilic Factor (Human).

## INDICATIONS AND USAGE

Antihemophilic 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 hemophilia A or acquired Factor VIII deficiency.[3] Antihemophilic Factor (Human), Profilate® Heat-Treated is not indicated in the management of bleeding in patients with von Willebrand's disease.

## CONTRAINDICATIONS

None known.

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 Antihemophilic 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 transmitted through this product.

## PRECAUTIONS

### GENERAL

Antihemophilic 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. Rarely, other patients acquire similar inhibitors. The management of patients with inhibitors requires careful monitoring, especially if surgical procedures are indicated.

In patients with inhibitors, the response to Antihemophilic Factor (Human), Profilate® Heat-Treated may be much less than would otherwise be expected and larger doses are often required. Patients with high inhibitor levels may not respond to Antihemophilic Factor (Human), Profilate® Heat-Treated at all.[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.

### PREGNANCY CATEGORY C:

Animal reproduction studies have not been conducted with Antihemophilic Factor (Human), Profilate® Heat-Treated. It is also not known whether Antihemophilic Factor (Human), Profilate® Heat-Treated can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Antihemophilic Factor (Human), Profilate® Heat-Treated should be given to a pregnant woman only if clearly needed.

## 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 Antihemophilic Factor (Human), Profilate® Heat-Treated.[10] Adverse reactions may be on an allergic basis. If a reaction is noted and the patient requires additional Antihemophilic Factor (Human), Profilate® Heat-Treated, product from a different lot should be administered.

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

Antihemophilic Factor (Human), Profilate® Heat-Treated does contain blood group 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 hemolysis and falling hematocrit. Should this condition occur, thus leading to progressive hemolytic anemia, the administration of serologically compatible type O red blood cells should be considered.

## DOSAGE AND ADMINISTRATION

Antihemophilic Factor (Human), Profilate® Heat-Treated must be administered intravenously within three hours following reconstitution with the diluent supplied. Antihemophilic 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.

[illegible] activity is expressed in International Units (I.U.). One unit approximates the activity in one ml of plasma. The following formula provides a guide of dosage calculations;

Number of AHF units required = Body weight in lbs x 20 x Desired increase in Factor VIII percentage

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

or

Number of AHF units required = Body weight in kg x 44 x Desired increase in Factor VIII percentage

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



Mild to moderate hemorrhages may usually be treated with a single administration sufficient to raise the plasma AHF level to 20 to 30 percent. In the event of more serious hemorrhage 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 postoperatively. 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 hemorrhages, Antihemophilic 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**

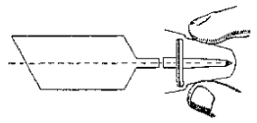
1. Warm diluent and concentrate bottles to at least room temperature (but not above 37°C).
2. Remove plastic flip-off cap from the diluent bottle.
3. Swab the exposed rubber surface with alcohol. Do not leave excess cleaning agent in indentation on stopper.
4. Remove all covering from one end of a double ended needle. Insert this exposed end of the needle through the depression in 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 filter spike will retain particles and the labeled potency will not be reduced.

### ADMINISTRATION

**By Syringe:**

**USE ASEPTIC TECHNIQUE**

1. Peel cover from filter spike package.
2. Remove protective cover from sterile disposable plastic syringe (not included).
3. Securely install the syringe into exposed fuer inlet of the filter spike using slight twisting motion.
4. Remove filter spike from blister-pak cup.



SYRINGE FILTER SPIKE