NOT FOR PUBLICATION

COMMERCIAL - IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

Sub-Committee on Biological Substances

	PL/0037/0071
Report by	Dr. D.P. Thomas
Meeting	November 1974
Therapeutic Class	Blood Product
Date Received	23-8-74

MEDICINES ACT 1968 - APPLICATION FOR A PRODUCT LICENCE

Summary and Report

1. PRODUCT SUMMARY

1.1. Name of Product: ANTIHAEMOPHILIC FACTOR (HUMAN)

1.2. Description: Lyophilized powder containing dried Human Antihaemophilic Factor. (to be reconstituted with supplied diluent).

1.3. Licence to be held by: Abbott Laboratories Ltd.,
Queenborough,
Kent.

1.4. Period of Validity: 5 years

1.5. Manufacturer: Abbott Scientific Products Division,
Abbott Laboratories,
5555 Valley Boulevard,
Los Angeles, California 90032, U.S.A.

1.6. Proposed Method of Sale: Through Supply Division of the Department of Health and Social Security.

1.7. Consideration of this application by other Sub-Committees Not referred

2. CLINICAL USE:

2.1 Recommended clinical use:

Therapy of Haemophilia A (Classical Haemophilia).

2.2 Route of Administration:

Intravenous

2.3 Recommended Dosage:

The dosage must be individualised according to the weight of the patient, the severity of the bleeding, the severity of his blood condition, the source of bleeding, inhibitors present (if any) and other factors as determined by the managing physician or surgeon.

The clinical effect on the patient is the most important factor in the evaluation of adequacy of therapy. It may thus be necessary to administer more Antihaemophilic Factor (Human) AHF that would be estimated in order to obtain the desired result. The dosage requirements of AHF when inhibitors are present are extremely variable, and the dosage can only be determined by the clinical response. Occasionally, low increments of AHF in patients with AHF inhibitors may suffice to produce satisfactory clinical responses.

3. STANDARD PROVISIONS:

No exemption is required from any of the standard provisions.

4. MANUFACTURE AND ASSEMBLY:

4.1 The manufacturing process is summarised in the following flow-sheet:-

Plasmapheresed Quick-Frozen Plasma

↓

Plasma Thawing and Pooling and Centrifuging ← Plasma (AHF-free) (To be frozen or processed)

↓

Wash and Suspend Cryo in Glycine extract solution; centrifuge

↓

Recons & Suspend Cryo in Citrated Saline solution; centrifuge

↓

Sterile Filtration

↓

Sterile Fill and Freeze

↓

Lyophilise

↓

Aseptic Stoppering and Vacuuming

4.2 (i) Collection of blood:

The Source Plasma (Human) used in the manufacture of the product

is collected by the United Biologics Donor Centres, owned by Abbott Laboratories. On November 20th, 1973, the United States Food and Drug Regulations for Source Plasma (Human) became effective. As required under these Regulations, applications for licence for Source Plasma (Human) for each location were submitted to the Food and Drug Administration before this date. These locations are in California, Arizona, Texas, Oregon and Washington.

4.3. Manufacture of Dosage Product:

Abbott Scientific Products Division,
Abbott Laboratories,
5555 Valley Boulevard,
Los Angeles, California.

5. QUALITY CONTROL

5.1 Quality control will be exercised as required under the U.S. Food and Drug regulations.

5.2 The licensee will be responsible for deciding if any batch of the product is of acceptable quality for marketing. This function will be exercised by the manufacturer, Abbott Scientific Product Division, at 5555 Valley Boulevard, Los Angeles, California.

6. Containers:

A 30 ml vial for the Antihaemophilic Factor (Human).
A 30 ml vial for the Sodium Chloride Injection, U.S.P.

Storage should be at temperatures between 2 and 8°C.

The product will be shipped directly to the consignee, by air from the U.S. to the U.K.

7.1 Labelling:

The label and the package enclosures will carry the following warning:
'Single dose container for intravenous administration'
'Discard unused contents'
'This product is prepared from units of human plasma which have been tested and found nonreactive for Hepatitis Associated Antigen. However, it is recognised that presently available methods are not sensitive enough to detect all units of potentially infectious plasma and the risk of transmitting hepatitis is still present'

A date of expiry will be stated corresponding to a shelf-life of 1 year at 2-8°C storage temperature.

8. Method of Sale and Supply:

The product will be made available through the Supply Division of the Department of Health and Social Security.

9. METHOD OF MANUFACTURE:

9.1 Specification of starting material: Plasma meets the requirment that each donation shall be individually tested, using the radio-immunoassay method, and found to be non-reactive for hepatitis associated antigen.

9.2 Plasma thawing, pooling and centrifuging:

The Quality Assurance-approved shipments of bottles of frozen plasma are removed from the freezer to the thawing room where they are decapped (but not unstoppered) and examined to sort out the HAA positives, those with missing and illegible bleeding numbers or those that are broken or damaged.

The plasma is thawed in circulating air at 4°C for a time which usually does not exceed 24 hours. The bottles are examined and those showing haemolysis or fat flotation removed. The retained bottles are emptied into the pooling tank with a swirling motion to dislodge precipitated material. The drainings are separately collected and are not used.

The mixture of cryoprecipitate and the liquid is passed through a Sharples super-centrifuge at a temperature of 1-5°C using a special nozzle and at a controlled specific flow rate.

The paste is scraped from the bowl, weighed and immediately put through the next stage.

9.3 Removal of residual plasma:

The weighed paste is ground into 7 times its weight of sterile glycine solution at 0-4°C.

The suspension is then gently agitated for 20 minutes at 0-4°C before being piped to a clean Sharples super-centrifuge through which it is passed under the same conditions as previously described.

The paste is scraped out, weighed and frozen at -65°C.

9.4 Reconstitution and clarification:

To the frozen cryoprecipitate is added citrated saline solution at a temperature not higher than 37°C and the containers are immersed in a water bath at 34-37°C.

The liquid is drained into a jacketed vessel below the grinder before passing the cryoprecipitate through the grinder.

The suspension is stirred for 40-50 minutes in the vessel at 34-37°C. A further 5 minutes stirring at high speed with a non-aerating stirrer is given.

The material is transferred to a source tank and further citrated saline solution added to bring the protein strength to 3.4%, and stirring continued for 20-30 minutes.

Using pressure supplied by sterile nitrogen, the suspension is filtered through a nylon bag into a source tank before passing through an ultracentrifuge (25,000 rpm) cooled to 5°C.

9.5 Sterile Filtration:

The solution is pumped through 0.8 micron prefilters before the 0.3 micron sterile filter and collected in a tank.

9.6 Filling and Freezing:

The sterile solution is dispensed by a Filomatic stainless steel syringe into 50 ml bottles. Total protein, calculated fill, activity units/ml, lead to an adjusted fill in ml/bottles to which the machine is adjusted.

The contents of the bottles are frozen by immersing half-way up in a dry ice-alcohol bath for 3 minutes. The bottles are transferred to a freezer. A Petri dish is placed before each operator, opened when filling starts and covered ½-hour later. These will be cultured by Quality Assurance.

9.7 Lyophilisation:

The material is lyophilised in a vacuum of 200 microns at a temperature never allowed to exceed 37°C. Bottles are sealed with processing caps immediately.

9.8 Stoppering and Evacuation:

The processing caps are replaced by the final stoppers with simultaneous evacuation to 30 in Hg. The bottles are sealed with an aluminium seal.

10. FINISHED PRODUCT

10.1 Marketing Formulation:

10.11 AHF Vial Active Constituent: Dried Human Antihaemophilic Fraction.

10.12 Sodium Chloride for Injection Vial: Sodium chloride, USP (9 mg/ml)
Water for Injection, USP

10.2 Quality Control:

10.21 Specification of Constituents:

10.22 Active Constituent: Plasma for fractionation meets the requirements that each donation shall be individually tested and found to be non-reactive for hepatitis-associated antigen. The Ausria (Abbott) test is used.

The donors meet the criteria of the regulations.

The blood from each donor is tested for syphilis (serological test), for blood group and for rH factor.

11. SELECTION AND SCREENING OF BLOOD DONORS

The controls applied in the collection of plasma for AHF manufacture are detailed in the copies of the forms used to collate the information on the medical history, physical examination and laboratory data of a proposed donor; the Donor medical history cards; the plasma donor list and daily donor rejection list. (see pages 29-37 of the submission).

12. IN-PROCESS CONTROLS:

12.1 Manufacture of AHF: Bottles of thawed plasma are examined for haemolysis and fat and those positive rejected.

During centrifuging, an examination of the out-going fluid for temperature and flow-rate is performed every 20 minutes.

The temperature of the glycine and cryo solution is measured every 5 minutes. During reconstitution of extracted cryo paste, the temperature of the citrated saline and the water bath temperature are checked every 20 minutes. The protein in the reconstituted solution is determined and the concentration adjusted to the desired figure. On the bulk final solution, the following tests are performed: Sterility, Activity, Total protein. The specification for the bulk solution is:

Sterility: Passes FDA Regulations.
Contents of Final Container: 200 units of activity per gram of protein.

12.2 Finished Product Specification:

AHF:- Sterility:
Safety:
Identity:
Pyrogen:
} Pass FDA regulations

Moisture: Does not exceed 2%
Isoagglutinins: Titre less than 1:32
Total Protein: Does not exceed 4 g/% upon reconstitution
Clottable Protein: Does not exceed 4 g % upon reconstitution (but less than total protein)
Thrombin: Does not clot
Activity: Minimum 5 AHF units/ml. 15 fold increase of normal human plasma/g protein.
Identity -
Labelled Final Specific Product Identification.
Container:
Before final release a labelled container from each batch is tested for identity.

13. ANALYTICAL CONTROLS ON FINAL PRODUCT:

AHF:-

13.1 Sterility: The sample consists of 10% of the containers in a batch of less than 200 containers, of 20 containers in a batch of more than 200. The containers are selected at approximately equal intervals during the production run. The powder is restored to approximately 25 ml with sterile diluent and the solution tested for sterility.

13.2 Safety: The sample is one container, randomly selected, per batch.

For each test two mice weighing approximately 20 g and 2 guinea pigs weighing approximately 350 g are injected parenterally, e.g. subcutaneously or intramuscularly. The test dose for each mouse is 0.5 ml and for each guinea pig 5.0 ml. If the injection is subcutaneous, bilateral injections may be made in abdomen area of mice and guinea pigs. A new 22 gauge disposable needle is used for each animal. The weights of mice and guinea pigs before injection and at completion of safety test are recorded.

The animals are observed for seven days and, should neither significant symptoms nor death occur in this period, the product tested passes general safety test.

13.3 Identity:

The sample is part of a sample container used for one of the tests.

This test is carried out by the Precipitin reaction by the interfacial technique, i.e. a small amount of antiserum is placed at the bottom of a tube and a layer of diluted antigen placed on top of this. The reaction, if any, occurs at the junction in the form of a "ring" of precipitate. (see p.15 of the submission for further details).

13.4 Pyrogens:

The sample is one container, randomly selected, per lot.

All final bulk tanks and a final container from each day's filling are tested for pyrogenic substances.

Three rabbits weighing 1500 g minimum (five rabbits, if a retest) with control temperatures not exceeding 39.8°C are used. The control temperatures before injection are the basis for determining if a substance is pyrogenic. 10 units AHF/kg rabbit body weight are injected. The sample fails if one half or more of all rabbits tested show a temperature rise of 0.6°C or more or if the average temperature rise of all rabbits used is 0.5°C or more.

13.5 Isoagglutinins:

The sample is one container.

Group A, and Group B prewashed test cells are used to test for saline isoagglutinins. Test cells with a month's dating are purchased from a commercial supplier. If an isoagglutinin titre of AHF is 1:32 or higher the lot must be clinically evaluated prior to release for distribution. (see p.18 of submission for details of the test).

13.6 Stability Reports:

The activity in the following subsections was measured by the thromboplastin generation test. The Thromboplastin Generation Assay has an experimental error of ± 20%. This has been allowed for in making the statements following.

At 32°C: Sample assayed over 13 weeks: The rate of loss of activity of this sample was constant over the period, and about a third of the activity was lost.

At 2-5°C: Assayed over 12 weeks; and it was concluded that there was no loss of activity over this period.

At -20°C: Samples were kept for 5-6 months. Measurements of activity were performed at the beginning and end only. There was no change in activity.

At 22°C: Sample was assayed over 13 weeks. Concluded that after stabilisation after 4 weeks at an activity of 85.5% of the original value, no further decrease occurred over the next 9 weeks.

At 4°C on production material (labelled final containers):

Out of 42 tests only 1 sample showed a loss of activity (over a period at least 3 times the stated shelf-life) of more than 20% of the initial activity when allowance is made for the error on both assays. There is also 1 result showing a gain of more than 20%.

13.7 Proposed Shelf-Life:

A shelf-life of 1 year at a storage temperature of 2-8°C is given.

13.8 Containers:

These are 30 ml glass vials, rubber-stoppered and aluminium sealed.

13.9 Assay of Factor VIII (see p.42 et seq. of submission for details)

A modified thromboplastin generation time test (TGT), a two-stage technique, is the assay used for determining the concentration of Antihaemophilic Factor (Human) activity.

A coagulation timer, as a Fibrometer or equivalent, thermal prep block heating unit and automatic pipette are used for coagulation determinations.

A standard reference plasma is used (no details given of whether or not it is standardized against the International Standard).

14 Medical Comment

The blood used for the preparation of this Factor VIII concentrate is screened for HBAg by radioimmunoassay. Blood is obtained by plasmapheresis of commercial donors at 8 centres in the U.S.A. Insufficient information is given on the assay of Factor VIII, particularly in relation to whether or not the International Standard for Factor VIII is used in the assay.

The manufacturer in California has not been inspected by the Licensing Authority.

15. Recommendation

That a Product Licence be granted.