DEPARTMENT OF HEALTH

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PRO CLASS	PIECE NUMBER
BN116	53

(write BOLDLY in black chinagraph pencil or black crayon)

FILE REFERENCE DETAIL	Volume or Part.
MF 804/5	D

DATES COVERED (In years)
FROM 1975 TO 1975

SUBJECT OR TITLE
COMMITTEE ON SAFETY OF MEDICINES SUB-COMMITTEE ON BIOLOGICALS MEETING 12.11.1975 : AGENDA, MINUTES AND PAPERS

PRO CLOSURE LABEL
Affix if appropriate.

NOT FOR PUBLICATION

CONFIDENTIAL - IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

Sub-Committee on Toxicity, Clinical Trials and Therapeutic Efficacy

MEDICINES ACT 1968

APPLICATION FOR A PRODUCT LICENCE

Product Licence Number	PL/0231/0038
Date Received	7-4-75
Meeting	November 1975
Medical Assessment by	Dr Andrews
Pharmaceutical Assessment by	Mrs Pratt
Therapeutic Class	Factor VIII

Summary, Report and Recommendation

1. PRODUCT SUMMARY

1.1 Name: FACTORATE (FACTOR VIII)

1.2 Pharmaceutical form and active constituent(s): Single dose vial containing Lyophilized cake to be reconstututed with 25 ml sterile water for Injection USP prior to administration. The solution contains ≤ 5 AHF u/ml.

1.3 Licence to be held by: Armour Pharmaceutical Company Limited
Hampden Park
Eastbourne
Sussex

1.4 Period of validity: 5 years

1.5 Manufacturer: Armour Pharmaceutical Company
Kankakee
Illinois

1.6 Applicant's proposed method of sale: Prescription item only

1.7 Legal status:

1.8 Consideration by other committees: Date:

a. Sub-Committee on Toxicity and clinical trials: N/R

b. Sub-Committee on Chemistry, Pharmacy and Standards: N/R

2. PHARMACEUTICAL FORM

The product is a sterile, white to pale yellow lyophilised preparation of purified anti-haemophilic factor (human) in 50ml glass containers closed with grey butyl stoppers and having an aluminium seal. Supplied with a vial of diluent and sterile needles for reconstitution, withdrawal and injection.

3. CLINICAL USE

3.1 Recommended Clinical Use

Therapy of classical haemophilia (haemophilia A).

3.2 Route of administration

After reconstitution the product is administered by intravenous infusion or injection.

3.3 Recommended dosage

Each single dose vial is labelled with the number of AHF units which it contains and the following dosages are suggested:-

3.3.1 Overt bleeding

Initially 20 units/kg of body weight followed by 10 units/kg every 8 hours for the first 24 hours and the same dose every 12 hours for three or four days.

3.3.2 Muscle haemorrhages

(a) Minor haemorrhages in extremities or non-vital areas:

10 units/kg once a day for 2 or 3 days.

(b) Massive haemorrhages in non-vital areas:

10 units/kg by infusion at 12 hour intervals for 2 days and then once a day for 2 more days.

(c) Haemorrhages near vital organs (neck, throat, sub-peritoneal):

20 units/kg initially then 10 units/kg every 10 hours. After 2 days the dose may be reduced by half.

3.3.3 Joint haemorrhages

10 units/kg 8 hourly for a day, then twice daily for 1 or 2 days. 10 units/kg to be given prior to aspiration with additional infusions of 10 units/kg 8 hourly and again on the following day.

3.3.4 Surgery

Dosages of 30-40 units/kg body weight prior to surgery. After surgery 20 units/kg every 8 hours with close laboratory control to maintain blood level of AHF above 40% of normal for at least 10 days post-operatively. As a general rule the circulating AHF level will increase by 2% for every 1 unit of AHF activity injected per kg. The adequacy of treatment must be judged by the clinical effects.

3.4 Contra-indications and warnings

There are no known contra-indications to AHF but the risk of transmitting viral hepatitis is present since no completely reliable laboratory test is yet available for detecting the presence of hepatitis virus.

Factorate contains low levels of group A & B isohaemagglutinins and the possibility of intravascular haemolysis should be considered when large volumes are given to patients of blood groups A, B or AB.

4. STANDARD PROVISIONS

All standard provisions shall apply to the licence.

5. MANUFACTURE

5.1 AHF is prepared by fractionation of fresh human plasma from selected donors followed by purification and freeze drying.

5.2 Place of manufacture

Active constituents:

Armour Pharmaceutical Company
P.O. Box 511
Kankakee
Illinois 60901
USA

Metrix Clinical and Diagnostic Division
Armour Pharmaceutical Company
Chicago
Illinois 60616
USA

Storage at -20°C during quarantine prior to labelling and at 2-8°C after labelling:

Armour Pharmaceutical Company
P.O. Box 511
Kankakee
Illinois 60901
USA

6. LABELLING

Copies of the labels and package leaflet stating directions for use, contra-indications and warnings is to be found at page 49, volume 2.

7. CHEMISTRY AND PHARMACY

7.1 Method of manufacture

Blood is drawn from acceptable donors by licensed physicians and the plasma obtained using plasmapheresis techniques must conform in all respect to the applicable requirements for source of plasma (human) defined in the USA code of Federal Regulations. This applies to licensed and unlicensed clinics. A copy of these are not included in the submission. Adequate records detailing the medical history of the donor, all physical examinations given him and appropriate release statements are kept for a recommended period of 12 years.

The supplier has agreed to provide plasma containing no additives other than citrate, acid citrate dextrose or citrate phosphate dextrose [illegible] anticoagulant solution drawn from adult humans by plasmapheresis [illegible] have not been hyperimmunized to produce specific antibodies (unless mutually agreed with Armour Pharmaceutical Company), and whose physical examination on the day of blood collection is found to be satisfactory. Donors with a history of viral hepatitis or exposure to hepatitis are excluded.

7.2 Plasma properties

The plasma is:

1. Substantially free from red blood cells
2. Contains no more than 50mg of haemoglobin per 100ml
3. Has a total protein content of not less than 5.5%
4. Is free of bacterial or pyrogenic contamination
5. Is packed in plastic or glass in volumes agreed by the Armour Pharmaceutical Company and the supplier.
6. Is stored and shipped below -20°C
7. Is free of hepatitis B antigen as tested on individual units by Radio-Immune assay.

7.3 Preparation of Factor VIII

Stage 1: Frozen plasma is removed from the collection bag by thawing, crushed and pooled and allowed to reach 3°C. Samples are taken and tested for freedom from hepatitis associated antigen.

Stage 2: The cryoprecipitate is removed from the pool and dissolved in buffer solution containing glycine, sodium chloride and sodium heparin.

Stage 3: The buffered cryoprecipitate is treated with sterilized non-reactive aluminium hydroxide to remove non active protein and centrifuged. The centrifugate is buffered with sodium citrate and sodium heparin, filtered, sterile filtered, vialed and lyophilised.

Stage 4: Final product is tested for freedom from hepatitis associated antigen.

8. QUALITY CONTROL

8.1 Quality control checks are made at each stage in the process (see section 8) and are listed as follows:-

a) Pyrogen tests
b) Determination of aluminium oxide
c) Sterility tests
d) Tests for non-specific agglutinins
e) Quantitative determination of airborne bacterial and mould contamination
f) Determination of bacteriostatic and fungistatic properties of products to be tested for sterility

(g) Microscopic examination of bacteria

(h) Determination of protein binding capacity

(i) Mammalian protein species identification

(j) Thromboplastin generation test - Results are expressed in terms of relative potency in the health standards by tests done in duplicate or triplicate and each result should agree within 10% of the average.

(k) Safety tests for normal serum albumin

(l) Biuret assay for total protein content of cryoprecipitated antihaemophilic globulin

(m) Determination of clottable protein

(n) Atomic adsorption analysis of aluminium in antihaemophilic factor

(o) Determination of heparin content

(p) Solution time for antihaemophilic factor (human) lyophilised

(q) Hepatitis associated antibody (Ausria II-125-Abbott)

Although the tests are adequately described some of them are laid down by the USA authorities and are not the same as those carried out in the United Kingdom.

8.2 Specification tests applied

8.2.1 Crude cryoprecipitate specifications

Total protein - not more than 5mg per AHF unit
Heparin - not more than 2 units/ml of reconstituted products
Solution time - readily soluble within 30 minutes in full volume of diluent.

8.2.2. Finished product specifications

Test	Specification
AHF Potency	Minimum of 5 AHF U/Recon. ml. + Minimum of 125 AHF U/Vial
Heparin Potency	Maximum of 2½ U/Recon. ml. + Maximum of 62.5 U/Vial
Total Protein	----
Total Protein/AHF U.	Maximum of 5mg/AHF U.
Aluminium	Maximum of 5 ppm
Moisture	Maximum of 2%
Identity	Human - Positive Bovine - Negative Porcine - Negative
Safety	Passes
Sterility	Passes
Pyrogen (10 AHF U/Kg)	Passes D.B.S. Standards
Solution Time	Maximum of 30 minutes
Isoagglutinin Titre	Maximum of 1:512

13. MEDICAL COMMENT

It is not quite clear who is the supplier of the donated plasma and it would appear that this could be a number of units(licensed and unlicensed) which work to FDA standards. It is also not clear whether the tests for hepatitis surface antigen is carried out on individual donations at the time of donation or during the routine examination of patients undergoing plasmapheresis. The company have been asked for information on this point together with a request for clarification of the place where quality control tests are carried out. It would appear that the manufacture of the product is satisfactory though the manufacturer has not as yet been inspected. The stability data provided at what is claimed to be 2-8°C does not show the time spent at any of the intermediate temperatures and it would be better if the shelf life is limited to 2°C.

It is recommended that subject to approval of the quality control situation that a product licence be granted.

R D Andrews
16.10.75

There were no significant abnormalities noted in the laboratory studies which were:-

Antihaemophilic factor activity
Thromboplastic time
Prothrombin time
Haemoglobin
Haematocrit
Serum transaminase
Serum haptoglobin

There were no subjective side effects

The highest Factor VIII level obtained was 50% immediately post infusion and the highest level 24 hours post infusion was 8%. 4 patients had an inhibitor against Factor VIII and failed to develop a significant rise. 4 patients had a fall in haematocrit 24 hours after infusion but no significant laboratory changes were noted.

11.2 Evaluation of AL-1067 by J Lazerson, Childrens' Hospital, Stanford and J Pool, Stanford University School of Medicine, Palo Alto, California

Dr Lazerson conducted 17 trials in 13 patients with established Haemophilia A, ranging in age from 6-26 years and from 19-70kg in weight. AL-1067 was administered at 20 units/kg. A number of laboratory studies were made and the investigator was satisfied with the safety and efficacy of the Factor VIII used.

11.3 Evaluation of AL-1067 by G R Honig, University of Illinois

7 patients with established haemophilia presenting with acute haemathrosis aged 3-14 years and weighing 16-64kg received AL-1067. The treatment was effective as judged clinically and as demonstrated by improvement in circulating levels of Factor VIII. Adverse effects were minimal and fibrinogen levels increased immediately after infusion (150-400mg%) in 3 patients. 24 hour levels had returned to or below initial values. Clinical benefits were clear in 6 of 7 patients but in the 7th patient there was difficulty in controlling haemorrhage (epistixis).

12. PUBLISHED PAPERS

The following papers are included in the submission:-

1. Treatment of Classic Haemophilia: The use of fibrinogen rich in Factor VIII for haemorrhage and for surgery

   The New England Journal of Medicine 1961.

2. Antihaemophilic Factor VIII in Haemophilia

   Journal of American Medical Association 1970.

3. Treatment of Haemophilia with Factor VIII concentrates

   The New England Journal of Medicine 1968.

These papers show that fraction 1 rich in Factor VIII is effective for replacement therapy of classical haemophilia uncomplicated by Factor VIII inhibitor states. Surgical procedures were successfully performed on 5 patients.

This is in accord with the extensive literature provided in the Travenol Hemofil application.

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