JH/ 15	COMMERCIAL IN CONFIDENCE APPLICATION FOR A PRODUCT LICENCE	NUMBER: PL 0231/0072 PRODUCT NAME: HEAT TREATED HIGH POTENCY FACTORATE
PROPOSED LICENCE HOLDER: Armour Pharmaceutical Co Ltd St Leonards House St Leonards Road Eastbourne East Sussex BN21 3YG		THERAPEUTIC CLASSIFICATION: Blood Product RECEIVED: 22.2.84 P.S.M: 12.3.84 MEETING: 4 July 1984 COMMITTEE ON: Safety of Medicines
MANUFACTURER OF DOSAGE FORM: Armour Pharmaceutical Company PO Box 511 Kankakee Illinois 60901 USA		SUB-COMMITTEE ON: Biologicals CONSIDERATION BY OTHER COMMITTEES: -
LEGAL STATUS: POM		ASSESSED BY: Dr K Fowler and Dr J Purves
SALE/SUPPLY: Hospitals		

1. Product Particulars

1.1	Name of Product:	Heat-Treated High Potency Factorate.
1.2	Pharmaceutical form:	Lyophilised powder for intravenous infusion after reconstitution with Water for Injections BP 250 i.v./vial; 500 i.v./vial; 1000 i.v./vial; 2000 i.v./vial
1.3	Active constituents:	Human Antihaemophilic Factor.
1.4	Uses:	Treatment of classical Haemophilia A.
1.5	Recommended dose and dosage schedule:	Dosage is in accordance with the needs of the patient. Full recommendations for general dosage are provided in the data sheet.
1.6	Contra-indications Precautions and Warnings:	No known contra-indications.

2. Data Sheet

The Company propose that the main body of the data sheet text used for High Potency Factorate (APPENDIX 1) will be retained for the heat treated product but the following statement will be included under 'Further Information', 'Experimental Studies have shown that heat-treatment of Antihaemophilic Fraction may remove or reduce the risk of transmission of non-A non-B hepatitis. Consequently this product has been subjected to heat treatment procedures during manufacture.

3. Background

3.1 General Information

Within the last year or so there has been evidence of a growing interest by Companies to heat treat Factor VIII, for a variety of reasons. This trend has no doubt been influenced as a result of the approval given by the FDA to American manufacturers of this product, to heat treat it under specified conditions.

CTX's have been granted to both Travenol and Armour Pharmaceuticals Co Ltd to undertake clinical studies using Factor VIII, which has been subjected to heat treatment, as follows:

i. Travenol - lyophilised form heat treated at 60°C for 72 hours.

ii. Armour - lyophilised form heat treat at 60°C ± 1°C for 30 hours and not more than 31 hours.

Product Licence applications to permit the inclusion of an additional heat treatment step have now been received from three manufacturers, namely Travenol, Hoechst and Armour (this application). The first of these companies applied to vary its existing Product Licence to include the additional heat treatment stage. This application was considered by the Biological Sub-Committee and the Committee on Safety of Medicines at their respective meetings in September of last year. The Main Committee was unable to recommend that the product licence for this preparation be varied as indicated in the application. The reason given are shown at APPENDIX 2. Toward the end of 1983 Hoechst applied for a product licence for heat treated Factor VIII. The heat treatment stage used in the manufacture of this product involves redissolving the Factor VIII in a "buffer with added stabilizers and heating at 60°C for 10 hours". This application was considered by the Biological Sub-Committee and the Main Committee at their respective meeting in March this year. The Main Committee advised the grant of a Product Licence for this preparation on condition that certain points raised were satisfactorily resolved. Details of these points are given at APPENDIX 3. This Product Licence has not yet been granted.

3.2 Information presented by Armour

The use of Dried Factor VIII Fractions in replacement therapy leads in some cases to the development of hepatitis (mainly hepatitis B or non-A non-B hepatitis) in certain patients as a result of occasional transfer of these viruses from infected donors. Diagnostic tests are available specifically for hepatitis B and although these are not infallible their use has led to a reduction in the incidence of the disease in haemophiliacs. No such test exists for detection of non-A non-B hepatitis virus(es) which thus cannot be screened. Pasteurisation has been used successfully as a means of destroying viruses in certain blood products (eg Albumin solutions) but early studies with Factor VIII solutions indicated a dramatic loss of potency during such procedures. More recently it has been established that heat-treatment of the finished, lyophilised product under controlled conditions can reduce the viability of, specifically, non-A non-B hepatitis virus without signficant effect on the potency of the material. The effect of this treatment on the viability of Hepatitis B virus is less clear and studies indicate that heat treatment is not effective. Nevertheless the possibility of achieving reduction of risk of transmission of non-A, non-B hepatitis by heat treatment is considered to be of significant advantage since this, coupled with the screening tests already available and used for detection of hepatitis B provides improved safety potential in therapy with these products. Heat treated Factorate products are currently undergoing registration in the United States and the heat-treated High Potency product is already on sale in Germany.

DOSAGE FORM

FORMULATION(S)		COMMENT
Description : Page(s) - 11		
Vial containing a white to pale yellow lyophilised cake for reconstitution with sterile 'water for injections'.		
Complete formula : Page(s) - 11		
ACTIVE CONSTITUENT	PER VIAL	
Dried Human Antihaemophilic Fraction	Nominal, 250, 500, 1000 and 2000 i.u.	Molarity of other constituents in existing licence (PL 0231/0044)
OTHER CONSTITUENTS		
Glycine USP	0.2M	0.31 Molar
Sodium Chloride USP	0.04M	0.15 Molar
Sodium Citrate USP	0.04M	0.01 Molar
Sodium Heparin USP	nmt 1 unit/ml (reconstituted solution)	NMT 30 units/vial
Container(s) : Page(s) - 11		
VIALS : Type 1 glass (30ml, 50ml, 50ml 100ml) CLOSURES: Grey butyl rubber stopper with an aluminium sea.		
MANUFACTURE	**Page(s) - 12**	
Details of the Extraction process for Antihaemophilic Fraction are provided under Section 8 of Part II Addendum of this application. The bulk finished material is sterilised by filtration through Millipore or Pall 0.22μ sterilisation filter assemblies.		
In each case the assembled filter housing are autoclaved at 126°C for 45 minutes before use and the filtered bulk solution is collected into a stainless steel bulk receiver tank previously autoclaved for 60 minutes at 121°C.		Details have not been given of: i. sterilization of containers ii. freeze-drying process iii. in-proces moisture limit.
The clarification/sterilisation assemblies are pre-wetted with sterile Water for Injections and a pressure hold test is carried out before filtration (cartridge assemblies). Sterile filtration is carried out under nitrogen (initially 0.5 - 1 psi increasing to approximately 5 - 6 psi) to maintain a steady flow.		What measures are taken to minimise the potential for contamination of the vial needs with organisms from the water bath?
Appropriate bubble point tests are conducted on both types of filter at the end of filtration.		
The finished, sterilised bulk liquid is filled aseptically into sterilised vials then frozen, dried from the frozen state under vacuum, stoppered under vacuum and sealed.		Where are the details of the validation process to justify the choice of this particular heat treatment process?
The finished vials are brought to 60°C ± 1°C in a water bath and held at this temperature for 30 hours and not more than 31 hours, before removal to quarantine prior to release by the Quality Control Department at Armour Pharmaceutical Company, Kankakee. Bulk unlabelled vials are shipped to the UK and labelling and packaging is carried out at the Company's manufacturing site at Hampden Park, Eastbourne.		

DOSAGE FORM	
QUALITY CONTROL	**COMMENT**
Specifications of constituents : Page(s) - 13	
Specifications controlling raw materials used in the manufacture of Heat-Treated High Potency Factorate are identical to those used in the manufacture of the non heat-treated product (PL 0231/0044). Vd II 1. Source Plasma (Human), Flash frozen P 1-9 2. Rehsorptan, aluminium hydroxide, sterile suspension 3. Sodium Heparin Injection USP 1,000 units/ml 4. Sodium Heparin Injection USP 5,000 units/ml 5. Sodium Heparin Injection USP 10,000 units/ml 6. Sodium Citrate USP reagent 7. Sodium Bicarbonate USP, pyrogen free 9. Amino-acetic acid USP (Glycine) 10. Glacial acetic acid Reagent grade USP	A medical view will be given on the suitability of the specifications cited for source plasma.
In-process control : Page(s) - 13	
None reported.	Specification approval sheets have not yet been signed and approved for use by the Director Quality Control Regulatory Affairs Manager Head of Pharmaceutical Sciences Chief Analyst Quality Control Manager
Finished Product Specification : Page(s) - 14	
Details of the specifications for the 250 i. ./vial and 2000 i. ./vial presentations are at pages of this report.	
DEVELOPMENT PHARMACEUTICS	
Formulation studies : Page(s) - 26	
The analytical control procedures applied to Heat-treated High Potency Factorate are identical to those already applied to the non-heated product licensed PL 0231/0044. 1. Experimental studies on heat-treated material have failed to show any detrimental effect attributable to the heat-treatment procedures. Copies of reports on these studies are supplied in Section 9 of this application. 2. Full analytical data after heat-treatment High Potency Factorate. The data are presented overleaf and indicate no significant departure from the results of similar assays on non-heat-treated material.	1. These studies included i. stability after heat treatment ii. effect on thorombin activation iii. immunochemical comparison of heat-treated Factorate. 2. Batch analyses of non-heat treated material should have been included to facilitate comparison.

Eastbourne England

QUALITY CONTROL DEPARTMENT
SPECIFICATION

No.	848/1
Date	September, 1983
By	C.G. Blatchford
Page	1 of 3

HEAT-TREATED
HIGH POTENCY FACTORATE, 250 iu/vial
[DRIED FACTOR VIII FRACTION B.P.]

DESCRIPTION

A white to pale yellow lyophilised cake in a 30 ml vial closed with a brown non-traumatic flip-cap, for reconstitution with 10 ml Water for Injections B.P.

TEST	SPECIFICATION	METHOD
*Appearance	Complies with description and produces a clear solution on reconstitution.	
*Mammalian Protein	Human positive Bovine, ovine and porcine negative	351/K
Potency	Not less than: 200 iu/vial 20 iu/ml reconstituted	B.P.
*pH	6.8 - 7.4 reconstituted	53/K
Moisture	Not more than 0.5% w/w	43-0(K)
Aluminium	Not more than 50 µg per vial	995/K
Citrate	Not more than 55 m mol/L reconstituted	1402/K
Fibrinogen	Not more than: 120 mg/vial, (80% of total protein) 12 g/L reconstituted.	994/K
Hepatitis B_s Antigen	Negative	379/K or 1410/K
Heparin	Not more than 10 iu/vial	1073/K
Isoagglutinins	Not more than 1:256 without predilution and typically less than 1:64 when tested against Anti-A and Anti-B.	386/K or 1426/K
Total Protein	Not more than: 150 mg/vial 15 g/L reconstituted	993/K

Q.C. Manager GRO-C

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QUALITY CONTROL DEPARTMENT
SPECIFICATION

No.	848/1
Date	September, 1983
By	C.G. Blatchford
Page	2 of 3

HEAT-TREATED
HIGH POTENCY FACTORATE, 250 iu/vial
[DRIED FACTOR VIII FRACTION B.P.]

TEST	SPECIFICATION	METHOD
Sodium	Not more than 200 m mol/L reconstituted	1301/K
Solution Time	Not more than 20 minutes, typically less than 10 minutes	1343/K
Sterility	Passes Test	303/K
Abnormal toxicity		
Mouse	Passes Test	963/K
Guinea pig	Passes Test	[inject > than 538 iu/Kg]
Pyrogens	Passes Test	208 [10 iu/Kg]

*These tests are carried out at RHC (UK) Limited, Eastbourne.

Q.C. Manager GRO-C

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ARMOUR PHARMACEUTICAL COMPANY LIMITED

Eastbourne England

QUALITY CONTROL DEPARTMENT

SPECIFICATION

No.	849/1
Date	September, 1983
By	C. Blatchford
Page	1 of 3

Title: HEAT-TREATED
HIGH POTENCY FACTORATE, 500 iu/vial
[DRIED FACTOR VIII FRACTION B.P.]

DESCRIPTION

A white to pale yellow lyophilised cake in a 50 ml vial closed with a brown non-traumatic flip-cap, for reconstitution with 20 ml Water for Injections B.P.

TEST	SPECIFICATION	METHOD
*Appearance	Complies with description and gives a clear solution on reconstitution.	
*Mammalian Protein	Human positive Bovine, ovine and porcine negative.	351/K
Potency	Not less than: 400 iu/vial 20 iu/ml reconstituted	B.P.
*pH	6.8 - 7.4 reconstituted	53/K
Moisture	Not more than 0.5% w/w	43-D(K)
Aluminium	Not more than 100 µg per vial	995/K
Citrate	Not more than 55 m mol/L reconstituted	1402/K
Fibrinogen	Not more than 240 mg per vial (80% of total protein) 12 g/L reconstituted	1344/K
Hepatitis B_s Antigen	Negative	379/K or 1410/K
Heparin	Not more than 20 iu per vial	1073/K
Isoagglutinins	Not more than 1:256 without pre-dilution and typically less than 1:64 when tested against Anti-A and Anti-B.	386/K or 1426/K
Total Protein	Not more than: 300 mg/vial 15 g/L reconstituted	993/K

Q.C. Manager GRO-C

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QUALITY CONTROL DEPARTMENT
SPECIFICATION

No.	849/1
Date	September, 1983
By	C. Blatchford
Page	2 of 3

Title HEAT-TREATED
HIGH POTENCY FACTORATE, 500 iu/vial
[DRIED FACTOR VIII FRACTION B.P.]

TEST	SPECIFICATION	METHOD
Sodium	Not more than 200 m mol/L reconstituted	1301/K
Solution Time	Not more than 20 minutes, typically less than 10 minutes	1343/K
Sterility	Passes Test	303/K
Abnormal toxicity		
Mouse	Passes Test	963/K
Guinea Pig	Passes Test	[Inject >538 iu/Kg]
Pyrogens	Passes Test	208/K [10 iu/Kg]

* These tests are carried out at RHC (UK) Limited, Eastbourne.

8. Q.C. Manager GRO-C

QUALITY CONTROL DEPARTMENT

SPECIFICATION

No.	850/1
Date	September, 1983
By	C.G. Blatchford
Page	1 of 3

Title HEAT-TREATED
HIGH POTENCY FACTORATE, 1000 iu/vial
[DRIED FACTOR VIII FRACTION B.P.]

DESCRIPTION

A white to pale yellow lyophilised cake in a 50 ml vial closed with a brown non-traumatic flip-cap, for reconstitution with 30 ml Water for Injections B.P.

TEST	SPECIFICATION	METHOD
*Appearance	Complies with description, and gives a clear solution on reconstitution.	
*Mammalian Protein	Human positive Bovine, ovine and porcine negative	351/K
Potency	Not less than: 800 iu/vial 26.5 iu/ml reconstituted	B.P.
*pH	6.8 - 7.4 reconstituted	53/K
Moisture	Not more than 0.5% w/w	43-0(K)
Aluminium	Not more than 180 µg per vial	995/K
Citrate	Not more than 55 m mol/L reconstituted	1402/K
Fibrinogen	Not more than: 480 mg/vial, (80% of total protein,) 16 g/L reconstituted.	994/K
Hepatitis B_s Antigen	Negative	379/K or 1410/K
Heparin	Not more than 30 iu/vial	1073/K
Isoagglutinins	Not more than 1:256 without predilution and typically less than 1:64 when tested against Anti-A and Anti-B.	386/K or 1426/K
Total Protein	Not more than: 600 mg/vial 20 g/L reconstituted	993/K

9. Q.C. Manager GRO-C

ARMOUR PHARMACEUTICAL COMPANY LIMITED

Eastbourne England

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QUALITY CONTROL DEPARTMENT
SPECIFICATION

No.	950/1
Date	September, 1983
By	C.G. Blatchford
Page	2 of 3

Title
HEAT-TREATED
HIGH POTENCY FACTORATE, 1000 iu/vial
[DRIED FACTOR VIII FRACTION B.P.]

TEST	SPECIFICATION	METHOD
Sodium	Not more than 200 m mol/L reconstituted	1301/K
Solution Time	Not more than 20 minutes, typically less than 10 minutes	1343/K
Sterility	Passes Test	303/K
Abnormal toxicity		
Mouse	Passes Test	963/K
Guinea pig	Passes Test	[Inject > 538 iu/Kg]
Pyrogens	Passes Test	208 [10 iu/Kg]

* These tests are carried out at RHC (UK) Limited, Eastbourne.

10. Q.C. Manager GRO-C

QUALITY CONTROL DEPARTMENT
SPECIFICATION

No.	351/1
Date	September, 1983
By	C.G. Blatchford
Page	1 of 3

HEAT-TREATED
HIGH POTENCY FACTORATE, 2000 iu/vial
[DRIED FACTOR VIII FRACTION B.P.]

DESCRIPTION

A white to pale yellow lyophilised cake in a 100 ml vial closed with a brown non-traumatic flip-cap, for reconstitution with 60 ml Water for Injections B.P.

TEST	SPECIFICATION	METHOD
*Appearance	Complies with description and gives a clear solution on reconstitution.	
*Mammalian Protein	Human positive Bovine, ovine, and porcine negative.	351/K
Potency	Not less than: 1600 iu/vial 26.7 iu/ml reconstituted	B.P.
*pH	6.8 - 7.4 reconstituted	53/K
Moisture	Not more than 0.5% w/w	43-0(K)
Aluminium	Not more than 300 µg per vial	995/K
Citrate	Not more than 55 m mol/L reconstituted	1402/K
Fibrinogen	Not more than: 960 mg per vial (80% total protein) 16g/L reconstituted	1344/K
Hepatitis B_s Antigen	Negative	379/K or 1410/K
Heparin	Not more than 50 iu per vial	1073/K
Isoagglutinins	Not more than 1:256 without pre-dilution and typically less than 1:64 when tested against Anti-A and Anti-B.	386/K or 1426/K
Total Protein	Not more than: 1200 mg/vial 20 g/L reconstituted.	993/K

Q.C. Manager GRO-C

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ARMOUR PHARMACEUTICAL COMPANY LIMITED

Eastbourne England

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QUALITY CONTROL DEPARTMENT
SPECIFICATION

No.	351/1
Date	September, 1983
By	C.G. Blatchford
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HEAT-TREATED
HIGH POTENCY FACTORATE, 2000 iu/vial
[DRIED FACTOR VIII FRACTION B.P.]

TEST	SPECIFICATION	METHOD
Sodium	Not more than 200 m mol/L reconstituted	1301/K
Solution Time	Not more than 20 minutes, typically less than 10 minutes	1343/K
Sterility	Passes test	303/K
Abnormal toxicity		
Mouse	Passes test	963/K
Guinea Pig	Passes test	[Inject >538 iu/Kg]
Pyrogens	Passes test	208/K [10 iu/Kg]

* These tests carried are carried out at RHC (UK) Limited, Eastbourne.

12.

GRO-C

Manager

DOSAGE FORM

DEVELOPMENT PHARMACEUTICS

Formulation studies : Page(s) - 26 (Continued)

3. Additional studies have been conducted on heat-treated High Potency Factorate in Germany where the product is already on sale through the heat-treatment process is applied to the standard product at Armour Pharma, Eschwege, Germany. A translation of the findings of a variety of tests applied to a batch of material before and after heat-treatment is attached (see next page).

4. Additional supporting evidence that heat-treatment does not affect Factorate material is provided by the results of analyses of three batches of Factorate (PL 0231/0038), before and after heat-treatment, copies of which are attached. These batches are destined for use on clinical studies conducted under CTX 0231/0070A (see two pages on).

5. As Factorate products are administered intravenously and the site of action is in the circulation, the material is delivered directly to its site of action and bioavailability considerations are not considered relevant.

3. what are the criteria of this heat treatment.

4. Using the criteria cited!

HF FACTORATE - Analysis before and after heat-treatment
(study conducted at Armour Pharma, Germany)

Batch No.: V31603

PARAMETER	BEFORE HEAT-TREATMENT	AFTER HEAT-TREATMENT
AHF Potency 2 stage assay	220iu/vial	220iu/vial
1 stage assay	190iu/vial	190iu/vial
Chromatography:		
HPLC	Separation into 7 peaks with icentical qualitative and quantitative profiles	
CAF Electrophoresis	Identical pattern	
UV Spectrum	No new absorption peaks following the treatment.	
Solution Time	4 minutes	4 minutes

COMPARISON OF ANALYSIS OF FACTORATE PRE AND POST HEAT TREATMENT

Test	X23102		X24302		X25203	
		Heat Treated		Heat Treated		Heat Treated
Assay	200	195 (190)	200	225 (220)	200	210 (205)
Freedom from Abnormal Toxicity	Pass	Pass	Pass	Pass	Pass	Pass
Pyrogens	Pass	Pass	Pass	Pass	Pass	Pass
Heparin iu/vial	3	4	2	5	2	6
Total Protein mg/l	9.7	14.5	12.3	16.4	19.5	22.4
Clottable Protein mg/l	6.6	6.4	6.9	7.3	9.8	11.4
pH upon reconstitution	7.5	7.4	7.5	7.3	7.6	7.3
Solution time min	3	2	3	3	3	6
Issoagglutinins Anti-A	1:32	1:16	1:1	No measurable Titre	1:128	1:128
Anti-B	No measurable Titre	No measurable Titre	1:8	1:8	1:32	1:16
Hepatitis B_s Antigen	Negative	Negative	Negative	Negative	Negative	Negative
Citrate mM/litre	6	7	12	8	16	10
Moisture %	0.1	0.3	0.0	0.2	0.1	0.2

DOSAGE FORM
STABILITY
Batches examined : Page(s) - 32-39
V 28602 (A 1607 - 024) V 44106 (A 1607 - 020)

Conditions of Storage	Results
1. Refrigerated (2-8°C) 2. Room Temperature (15-30°C) 3. Elevated Temperature (35°C)	A. Potency B. Potency 3-Hour Post Reconstitution C. Solution Time/Appearance

CONCLUSIONS MADE BY COMPANY

The Company has concluded that the stability data indicates that heat-treatment produces a small loss in potency although it is difficult to quantify this loss owing to possible effects of other variables in the assay. Assay results of heat treated product indicates the material is stable stored at refrigeration temperatures. Accelerated stability data (35°C/6 months) indicates that the material does not lose potency significantly.

It is concluded that, apart from a slight initial drop in potency as a result of heat treatment, the conditions of heat treatment do not affect the stability or shelf-life of the product.

Chemistry of the Drug Substance	Comment
1. Pharmaceutical Name: 1.1 Dried Human Antihaemophilic Fraction BP. 1.2 U.S. Adopted Name : Antihemophilic Factor. 1.3 Other Names : Factorate High Potency Factorate	
2. Description 2.1 A white to pale yellow lyophilised cake.	
3. Method of Manufacture (Pages 42 - 45 of application) Brief details of the method of manufacture of this product have been copied at pages of this report. Essentially the method of manufacture is that which has been seen before for High Potency Factorate (PL 0231/0044), but with one additional step and that is, Heat treatment of the product, which is lyophilized and sealed in vials under vacuum, in a water-bath at 60°C ± 1° for thirty hours.	
4. Development Chemistry The Company has introduced this heat-treatment process "as a potential means of reducing transmission of non-A, non-B hepatitis virus" and decided "In view of this additional process and the potential effect such heat-treatment might have on the Factor VIII molecule, a series of experiments have been carried out to compare the heat-treated material with non-heat-treated material. Three such studies have been undertaken details of which are shown in the application, 4.1 Stability After Heat-Treatment (P 46 - 48) It is stated by the Company (P 48) that "previous experiments have indicated that heating Generation II Factorate to 60°C for 24 hours may not be sufficient to destroy Hepatitis B. Therefore, a longer period of heating may be necessary. This experiment is designed to detect changes, if any, in AHF activity when Factorate is heated at 60°C/72 hours in the dry state.	Page 48 should be read before Page 47!!! The objectives and conclusions of this experiment are not entirely clear : very little can be concluded from data presented. It is of interest to note that the Co. considered "60°C/24 hours may not be sufficient to destroy Hepatitis B".

8. MANUFACTURE

The basic manufacturing procedure is essentially the same as that used for the existing High Potency Factorate Product (PL 0231/0044) as described in our variation application submitted in February 1980.

After lyophilisation and sealing of the vials, the vials are brought to 60°C ± 1°C in a water-bath and held at this temperature for a period of thirty hours.

For completeness the full manufacturing description as depicted in our previous variation, together with the heat-treatment stage are included as follows:

High Potency material is manufactured from fresh frozen, human plasma which, when tested, complies with the Raw Material Specification for source plasma (Specification 3029 supplied separately in a manual (dated October 1983) for specification and methods common to all Factorate products) and is negative for Hepatitis B surface antigen activity. A cryoprecipitate is isolated from thawed human plasma and dissolved at 25°C ± 5°C in glycine-saline buffer containing not more than 3 u/ml Sodium Heparin USP. The pH of the solution is adjusted to 6.4 with 0.1 M acetic acid, cooled, centrifuged and pH adjusted to 6.9 with 0.5 Sodium hydroxide solution. Impurities are adsorbed onto an added quantity of aluminium hydroxide suspension, subsequently removed by centrifugation at approximately 15°C after which the centrifugate is clarified by filtration. The clarified bulk material is mixed with sodium citrate and sodium chloride and stirred to dissolve the latter. The bulk is cooled to 0°C and 95% Alcohol added. After alcohol addition the bulk is cooled to -1 to -2°C and stirred for a minimum period of 20 minutes before centrifugation to remove precipitate. The precipitate is resuspended in citrate/saline/glycine buffer and held frozen for a minumum period of six hours before rethawing at 34°C and bringing to final volume with saline glycine buffer.

The pH of the solution is adjusted to 5.8 - 5.9 with 0.5 M acetic acid at controlled room temperature. The solution is cooled to approximately 3°C, held at this temperature for ninety minutes and centrifuged. The supernatant is filtered through a series of Millipore filters or a Pall cartridge assembly to clarify. The pH of the finished solution is adjusted to 7.0 with 0.5M NaOH and the solution sterile filtered through Millipore or Pall cartridge assemblies with smallest pore size 0.22μ.

FLOW DIAGRAM

Manufacturing Process for Antihaemophilic Factor (Human), (High Potency)

PHASE A - Collection and Storage of Human Plasma

↓

PHASE B - Isolation of Cryoprecipitate

a) Thawing at $0^{\circ}C \pm 2^{\circ}C$
b) Centrifugation at $1^{\circ}C \pm 2^{\circ}C$ ⟶ Cryo-Poor Plasma Supernatant

↓

PHASE C - Dissolution of Cryoprecipitate in Glycine-Saline Buffer Containing Heparin

a) pH adjustment
b) Centrifugation/Filtration ⟶ Precipitate discarded
c) pH adjustment

↓

PHASE D - Aluminium Hydroxide Adsorption (Sterile 2% Suspension Added)

a) Storing at $15^{\circ}C \pm 5^{\circ}C$
b) Centrifugation and Filtration ⟶ Precipitate discarded

↓

PHASE E - Stabilisation and Alcohol Precipitation

a) Sodium Citrate, Sodium Chloride additions
b) Addition of Ethanol at $0^{\circ}C \pm 2^{\circ}C$

↓

PHASE F - Isolation of Precipitate by Centrifugation ⟶ Discarded Supernatant at $0^{\circ}C \pm 3^{\circ}C$

↓

PHASE G - Resuspension of Precipitate in Citrate-Saline-Glycine Buffer

a) pH adjusted 7.0 ± 0.2 (below $-40^{\circ}C$)

↓

PHASE H - pH adjustment followed by cooling and filtration through membrane filter.

a) pH adjustment to 6.8 ± 0.8 (at $15-30^{\circ}C$)
b) Cool solution to $8^{\circ}C \pm 5^{\circ}C$ ⟶ Precipitate discarded
c) pH clarified solution adjusted to 7.2 ± 0.4 with 0.5 M Sodium Hydroxide

↓

PHASE I - Clarification through a Membrane Filtration Assembly

↓

(see next page)

FLOW DIAGRAM (cont.)

PHASE J - Sterile Filtration into Sterile Holding Tanks
(Sample submitted for Bulk Sterility Testing)

↓

PHASE K - Filling (Under Constant Positive Pressure)

↓

PHASE L - Lyophilisation (Under vacuum) and Sealing of Vials for Inspection and Storage at 2-8°C or colder.

↓

PHASE M - Heat-treatment in a water bath at 60°C ± 1° for thirty hours.

9. DEVELOPMENT CHEMISTRY

Heat-treated High Potency Factorate differs from the licensed High Potency Factorate product only in the heat-treatment process carried out on the finished product. This stage has been introduced as a potential means of reducing transmission of non-A, non-B Hepatitis virus. In view of this additional process and the potential effect such heat-treatment might have on the Factor VIII molecule, a series of experiments have been carried out to compare the heat-treated material with non heat-treated material. copies of reports of these experiments are provided in this section.

NB High Potency Factorate material is referred to as Factorate Generation II material in these studies as this is the trade-name for this product in the USA.

9.1. Stability After Heat-Treatment

Long-term stability studies on heat-treated High Potency Factorate are on-going and the results of testing after storage for up to one year are presented in the stability section of this application.

In addition to these results, an experiment has been conducted to determine the comparative potency of heated (60°C for 72 hours) and non heat-treated product for periods up to 25 days after reconstitution. The results of these tests are presented in study PFR-81-010 presented overleaf. No significant differences in potency were observed between the two products.

9.2. Effect on Thrombin Activation

Antihaemophilic Fraction is known to cause a pronounced increase in the activity of thrombin although the mechanism of this action is unknown. The attached report, PFR-82-050 investigates the comparative effects of heated and non heat-treated High Potency Factorate to determine whether heat-treatment has any effect on this action of Antihaemophilic Fraction. Assessments of relative activity by the one stage PTT assay indicated that there was no significant difference between the two materials.

9.3. Immunochemical Comparison of Heat-Treated Factorate

Immunochemical experiments have been carried out with rabbit plasma containing antibodies to heated and non heat-treated Factorate proteins, in order to determine whether heat-treatment has any demonstrable effect on these proteins. An account of one such experiment is provided under study No. PFR-82-043 attached. Evaluation of the results for the possible development of neoantigens as a result of heat-induced modification of protein structure indicated that this had not taken place.

Chemistry of the Drug Substance	Comment
	No validation study has been presented to justify the time/temperature chosen for the heat treatment.
4.2 Effect of Thrombin Activation (P 49 - 53) The objective of this experiment was to "determine whether conditions that may be suitable for pasteurisation of Factorate affect the characteristics of its activation by Thrombin".	
4.3 Immuno-chemical comparison of Heat-Treated Factorate (P 54 - 61). The objective of this experiment was a "heat Factorate in the drug state at 60°C for 24 hours and then immunochemically determine if the proteins have been altered by this treatment."	It should be noted that heat treatment for the product to be marketed is 60°C ± 1°C for 30 hours. P 58 two dimensional electrophoresis traces too poor to interpret! P 59 Gel diffusion results impossible to interpret. Note amended discussion on Page 6!! On Page 61 it is cited that "cross-over studies with the two antigen preparations and the various antisera essentially gave the spare IEP patterns. These results should be presented.
5. Impurities (P 62) The impurity profile of Heat-treated High Potency Factorate is predicted to be as the existing non heat-treated product. The experiments detailed in the previous section have failed to show the generation of any modified structure as the result of heat-treating. The finished product specifications for High Potency Factorate products include tests for aluminium citrate, heparin and sodium which are added during processing and traces of which are residual in the finished product. In addition endogenous impurities such as fibrinogen and isoagglutinins are also present and subject to assay. Where appropriate the limits of these impurities comply with the requirements of the BP monograph for dried Factor VIII Fration.	The Sub-Committee may wish to consider the suitability of the tests and results present in support of the Company's prediction.

Chemistry of the Drug Substance	Comment
6. Specification (P 63) The specification of the drug substance is the same as that presented for the finished dosage form, presented earlier in this report and given at Pages 14 -25 of the application.	It should be noted that the specification approval sheets at Pages 16, 19, 22 and 25 have not been checked and approved by any of the following: 1. Director, Ouality Control. 2. Regulatory Affairs Manager. 3. Head of Pharmaceutical Sciences. 4. Chief Analyst. 5. Quality Control Manager.

Pharmaceutical Comment

Much of the information presented in support of this application for a Product Licence has been supplied before in support of the licence application for High Potency Factorate and the subsequent variations to this licence.

However, on consideration of the volume of data supplied on ingredient specifications, it would appear that the specification for Source Plasma (Human) is not up-to-date eg FDA requirements of March 1983. Information presented on the other specifications appear adequate.

The Company has presented some background information on heat treated Factor VIII (3.2 of this report) and cited that "more recently it has been established that heat-treatment of the finished, lyophilized product under controlled conditions can reduce the viability of specifically, non-A and non-B hepatitis virus without significant effect on the potency of the material ..... improved safety potential in therapy with these products". In the absence of the citation of published papers to support these statements it was anticipated that supportive data would be found in the application.

Certain deficiencies have been detected in the application relating to the manufacture of dosage form: These are as follows,

i. details of the sterilization of containers, the freeze-drying process and the in-process moisture limit have not been included

ii. no details have been presented on the validation studies undertaken which justify the choice of the heat treatment process.

iii. the proposed specifications cited in the application have not been approved by senor company personnel.

iv. inadequate information has been presented in the Section on Development Pharmaceutics to support the significant change to the manufacturing process of Factor VIII.

Reference is made to experimental studies on heat treated material (see Drug Substance 4.1 to 4.3). From these experiments and the results obtained it has been concluded that the studies "have failed to show any detrimental effect attributable to the heat-treated procedures".

Analytical data has been presented on heat-treated Factor VIII. Results obtained are similar to those for non-heated material. However, this data is considered inadequate in two respects, namely quantity, the design of the study undertaken Experiments should have been undertaken to stress the product ie for greater periods of time and at higher temperatures.

The relevance of the Caerman study is obvious.

The statement that the "heat treatment does not affect Factorate material" (p.26) might be true using the criteria cited but are these parameters suitable to detect any change no matter how subtle it might be.

The total package of data presented at pages 45-61 on the 'Development Chemistry' relating to heat treated Factorate is considered inadequate as a justification that the heat treatment process chosen (60°/30 hours) is suitable for its intended purpose, without adversely effecting the integrity of the Factor VIII. The limited selection of studies undertaken, the objectives of these and conclusions drawn do not form a strong cohesive case in support of the inclusion of the additional heat-treatment step to the manufacturing process. This conclusion is drawn because,

i. no attempt has been made to show the scientific justification for chosing a) heat treatment at 60°/30 hours and b) heat treatment of the freeze-dried product.

ii. inadequate scientific evidence has been presented to confirm that the heat treatment has not adversely effected the product. In addition, some of the evidence presented relates to a product that has been heat treated at 60°/24 hours, not 30 hours which is the time period used for the product proposed for marketing.

iii. the Sub-Committee members may wish to consider the suitability of the method of heat treatment and the criteria of treatment, in view of the fact that micro-organisms can be protected from damage by heat, and other agents, by virtue of two factors, the dry state, and the protective nature of protein envelopes eg the viability of bacterial spores is conferred by these parameters. It is known that the efficacy of kill of sterilisation procedures is less when a dry heat method is used as opposed to a wet method (eg 150°C/ 1 hour, dry heat as 121°C/15 minutes wet heat).

It may be that if the Company's predictions are correct (p.26), that is, "experimental studies on heat treated material have failed to show any detrimental effect attributable to the heat-treatment procedures," then it may be ineffective in killing virus effectively throughout the product. No evidence has been presented on the efficacy of the heat treatment against product spiked with viruses!!!

Pharmaceutical Conclusion and Recommendation

The Sub-Committee members may on the evidence before them, on the grounds of quality, feel unable to recommend the grant of a product licence on the basis that,

1. justification is required for the inclusion and the choice of heat treatment used.

2. the heat treated product is adequately characterised supported by suitable data, which is clearly presented.

3. further details are required on the sterilization of containers, the freeze-drying process and the in-process moisture limit for the product.

June 1984 J PURVES

PRODUCT LITERATURE

1.1. Labelling and Package Insert

The label text for the product will be as that used for the existing product, High Potency Factorate (PL 0231/0044), except that the term 'Heat-treated' will be incorporated. The labelling will comply with the requirements of the BP monograph for Dried Factor VIII Fraction.

1.2. Data Sheet Text

It is proposed that the main body of the data sheet text used for High Potency Factorate (copy overleaf) will be retained for the heat-treated product but the following rationale will be included under 'Further Information':

'Experimental studies have shown that heat-treatment of Anti-Haemophilic Fraction may remove or reduce the risk of transmission of non-A non-B hepatitis. Consequently this product has been subjected to heat-treatment procedures during manufacture.'

HIGH POTENCY FACTORATE

PRESENTATION

Dried Human Antihaemophilic Fraction HIGH POTENCY FACTORATE is a stable lyophilised concentrate of Factor VIII (AHF, AHG) prepared from pooled human plasma. It conforms to the monograph for Dried Human Antihaemophilic Factor B.P.

Each vial contains the labelled amount of antihaemophilic activity in International Units (one International Unit is the activity equivalent to the average Factor VIII content of 1 ml aliquots of 167 samples of fresh normal plasma, as determined in an international collaborative study). Each vial also contains sufficient sodium chloride to make the reconstituted solution approximately isotonic when Water for Injections B.P. is added as directed.

USES

For use in therapy of classic haemophilia (Haemophilia A).

DOSAGE

HIGH POTENCY FACTORATE is for intravenous administration only. As a general rule one unit of Factor VIII activity per kg will increase by 2% the circulating Factor VIII level, and although dosage must be adjusted according to the needs of the patient (weight, severity or haemorrhage, presence of inhibitors) the following general dosages are suggested.

1. Overt Bleeding

Initially 20 units per kg of body weight followed by 10 units per kg every eight hours for the first 24 hours and the same dose every 12 hours for the next 3 or 4 days. For massive wounds, give until bleeding stops and maintain with 20 units per kg 8-hourly to achieve a minimum Factor VIII level of 40%.

2. Muscle Haemorrhages

(a) Minor Haemorrhages in extremities or non-vital areas: 10 units per kg once a day for 2 or 3 days.

(b) Massive Haemorrhages in non-vital areas: 10 units per kg by infusion as 12 hour intervals for 2 days and then once a day for 2 more days.

(c) Haemorrhages near vital organs (neck, throat, subperitoneal), 20 units per kg initially; then 10 units per kg every 8 hours. After 2 days the dose may be reduced by one-half.

3. Joint Haemorrhages

10 units per kg every 8 hours for a day; then twice daily for 1 or 2 days. If aspiration is carried out, 10 units per kg just prior to aspiration with additional infusions of 10 units per kg 8 hours later and again on the following day.

4. Surgery

Dosages of 30 to 40 units per kg body weight prior to surgery are recommended. After surgery 20 units per kg every 8 hours should be administered. Close laboratory control to maintain the blood level of Factor VIII above 40% of normal for at least 10 days post-operatively is suggested.

5. Dental Extractions

For simple extractions a pre-operative dose of 20 - 25 units per kg sufficient to raise the Factor VIII level to 50% should be given, followed by intravenous administration of tranexamic acid. For multiple extractions further doses of Factor VIII may be advisable 24 or 36 hours after the operation. (Dormandy 1977.)

RECOMMENDED RECONSTITUTION

Reconstitute HIGH POTENCY FACTORATE using 30 ml Water for Injections B.P. using standard aseptic precautions.

Warm both diluent and HIGH POTENCY FACTORATE vials to between 20°C and 30°C. Direct diluent down the side of the vial and gently rotate the vial until contents are dissolved. DO NOT SHAKE VIAL. Vigorous shaking will cause frothing and prolong the reconstitution time. Complete solution usually takes approximately 10 minutes. The solution is now ready for administration. If a gel forms on reconstitution, the preparation should not be used. The solution should be used within three hours of reconstitution.

ADMINISTRATION

Standard aseptic techniques should be used at all times

Intravenous Injection

Plastic disposable syringes are recommended with Factor VIII solution. The ground glass surfaces of all-glass syringes tend to stick with solutions of this type.

1. Attach a filter needle to a sterile disposable syringe. Insert filter needle into stopper of Factor VIII vial; inject air and withdraw the reconstituted solution from the vial.

2. Discard the filter needle and attach a suitable intravenous needle.

3. Administer solution by slow intravenous injection, at a rate comfortable to the patient, and not exceeding 2 ml per minute.

Intravenous Infusion

The infusion equipment used should comply with that described in sections 3 or 4 of British Standard 2463:1962, Transfusion Equipment for Medical Use.

1. Prepare solution of HIGH POTENCY FACTORATE as recommended under Reconstitution.

2. Attach suitable infusion set.

3. If more than one vial is to be administered to the same patient the infusion set may be transferred to a second vial.

4. When infusion of HIGH POTENCY FACTORATE is complete, the infusion set may be flushed with sterile isotonic saline to avoid loss of any of the reconstituted solution.

5. After use, discard infusion set, needles and vials together with any unused solution.

WARNING

Factor VIII is prepared from human plasma, each donation of which has been found negative for hepatitis B surface antigen (HBsAg) by the radioimmunoassay (RIA) method. In addition, each batch, after reconstitution as recommended, has been tested and found negative by the RIA method. However, since no completely reliable laboratory test is yet available to detect all potentially infectious plasma donations, the risk of transmitting viral hepatitis is still present.

SIDE EFFECTS

Products of this type are known to cause mild chills, nausea or stinging at the infusion site.

CONTRA-INDICATIONS

There are no known contra-indications to antihaemophilic fraction.

PRECAUTIONS

Factor VIII contains low levels of group A and B isohaemagglutinins. When large volumes are given to patients of blood groups A, B or AB, the possibility of intravascular haemolysis should be considered. Such patients should be monitored by means of haematocrit and direct Coombs test for signs of progressive anaemia.

PHARMACEUTICAL PRECAUTIONS

HIGH POTENCY FACTORATE is to be stored below 6°C. When stored as directed, it will maintain its labelled potency for the period indicated on the label.

LEGAL CATEGORY

P.O.M.

PACKAGE QUANTITIES

HIGH POTENCY FACTORATE is supplied in single dose vials (potency is stated on each vial label).

FURTHER INFORMATION

Haemophilia A, a hereditary disorder of blood coagulation occurring almost exclusively in males results in profuse bleeding in joints, muscles or internal organs as a result of minor trauma. The disease appears to be due to a deficiency of a specific plasma protein, antihaeomphilic factor, Factor VIII: HIGH POTENCY FACTORATE provides temporary replacement of the missing clotting factor.

Affected individual frequently require therapy following minor trauma. Surgery, when required in such individuals must be preceded by temporary correction of the clotting abnormality with fresh plasma transfusions, cryoprecipitate or by injections of Factor VIII concentrates. Advantages of the use of concentrates of Factor VIII are the avoidance of hyper-proteinaemia, overloading the circulatory system and possible kidney dysfunction resulting from large volume transfusions. Several different concentrations of Factor VIII have been used successfully. These range from Fraction I of Cohn to highly-purified poteny preparations. Dried Human Antihaemophilic Fractions - HIGH POTENCY FACTORATE is a purified preparation with lower levels of fibrinogen and other non-AHF proteins per international unit than "Intermediate Purity" AHF preparations.

PRODUCT LICENCE NUMBER

PL 0231/0044

PRODUCT LICENCE HOLDER

Armour Pharmaceutical Company Limited,
St. Leonards House,
St. Leonards Road,
Eastbourne,
East Sussex,
BN21 3YG

APPENDIX 2.

No:

PL 0116/0011

Company:

Travenol Laboratories Limited

Product:

Hemofil

Therapeutic Class:

Blood Product

Active Constituent:

Factor VIII

Main Committee 22/23.9.83

Advice

On the evidence before them the Committee on grounds relating to safety, quality and efficacy were unable to recommend that the product licence for this preparation should be varied as indicated in the application.

1. inadequate evidence of safety and efficacy was provided,

2. justification should be provided for the inclusion and choice of heat treatment,

3. the heat treated product was inadequately characterised,

4. in the event of the grant of a variation to the licence labels and data sheets should be amended to the satisfaction of the Secretariat.

Remarks to Licensing Authority

Promotional letters making unjustified claims on improved safety margins in respect of infection and A.I.D.S were seen by the Committee and strongly deprecated.

Remark to Company

Evidence of the long-term safety in haemophiliac patients of treated products such as this is regarded as an important pre-requsite of licensing.

APPENDIX 3.

No. PL 0086/0100 Coy. Hoechst UK Ltd Product Factor VIII HS Therapeutic Class Antihaemophilic Active Constituent Factor VIII 250 iu, 500 iu, 1000 iu per vial	Main Committee 22/23.3.84 Advice On the evidence before them the Committee advised the grant of a Product Licence for this preparation on condition that: 1. satisfactory information was provided on the heat-treatment process; this should include the identity and concentrations of added stabilising agents, 2. clarification was given on the electrophoresis data before and after heating, with special reference to the thermal degradation products of Factor VIII and clear statements were given on the change in Factor VIII potency, 3. the Finished Product Specification was amended to include:- i) a test with suitable limits for sodium, ii) a clear statement of the acceptance/rejection criteria in the microzone electrophoresis test, iii) an upper limit of Factor VIII activity of not more than 125% of the labelled amount. 4. suitable comparative results between the Behringwerke assay for Factor VIII and the BP 1980 assay were provided, together with confirmation that the Behringwerke standard was calibrated in IU against the WHO International Standard, 5. additional stability data were provided showing the results of tests for degradation products on storage, 6. confirmation was given that the air in the vial is removed or replaced by sterile oxygen free nitrogen, 7. an assurance was given that the Albumin would comply, if tested with all the tests in the BP specification, 8. biological evidence of the reproducibility of the inactivation process was provided, 9. the Data Sheet and Product Particulars were amended to the satisfaction of the Secretariat, with particular reference to: i) inclusion of a statement that the material was heat-treated; ii) no claims being made that the transmission of hepatitis B and non-A non-B hepatitis had been excluded; iii) no reference to AIDS being included except as a warning that blood products may transmit the syndrome,

No. PL 0086/0100 Cov. Hoechst UK Ltd Product Factor VIII HS Therapeutic Class Antihaemophilic Active Constituent Factor VIII 250 iu, 500 iu, 1000 iu per vial	10. the Batch Release procedure should apply, to include the provision of bulks and in-process samples. Remark Further studies on the effectiveness of the inactivation process should be undertaken.

ASTBOURNE ENGLAND

Document APPENDIX 4.

Product:

HIGH POTENCY FACTORATE
(GENERATION IIB)
HEAT-TREATMENT

STABILITY REPORT

Number	Date
	MAY 1983

Replaces

1. POTENCY

BATCH NO.	STORAGE TEMPERATURE °C	TESTING INTERVAL (MONTHS)	UNHEATED CONTROL		HEATED MATERIAL POTENCY		
			IU/VIAL	% INITIAL	IU/VIAL	% OF INITIAL UNHEATED CONTROL	% OF INITIAL UNHEATED CONTRO
8602	2 - 8°C	0	728	100	674	93	100
		1	-	-	706	97	105
		2	-	-	693	95	105
		3	-	-	703	97	104
		6	-	-	681	94	101
		12	648	89	630	87	93
	15 - 30°C	0	728	100	674	93	100
		1	-	-	692	95	103
		2	-	-	693	95	103
		3	-	-	686	94	102
		6	-	-	672	92	100
		12	642	88	637	88	95
	35°C	0	728	-	674	93	100
		1	-	-	718	99	107
		2	-	-	704	97	104
		3	-	-	690	95	102
		6	701	96	660	91	98

Product:

HIGH POTENCY FACTORATE
(GENERATION IIB)
HEAT-TREATMENT

STABILITY REPORT

Number	Date
	MAY 1983

Replaces

1. POTENCY (Cont.)

BATCH NO.	STORAGE TEMPERATURE °C	TESTING INTERVAL (MONTHS)	UNHEATED CONTROL		HEATED MATERIAL POTENCY		
			IU/VIAL	% INITIAL	IU/VIAL	% OF INITIAL UNHEATED CONTROL	% OF INITIAL UNHEATED CONTR
106	2 - 8°C	0	826	100	783	95	100
		1	-	-	798	95	101
		2	-	-	790	96	101
		3	-	-	775	94	99
		6	-	-	770	93	98
		12	783	95	747	90	95
	15 - 30°C	0	826	100	783	95	100
		1	-	-	784	95	100
		2	-	-	774	94	99
		3	-	-	778	94	99
		6	-	-	761	92	97
		12	776	94	741	90	95
	35°C	0	826	-	783	95	100
		1	-	-	796	97	102
		2	-	-	773	94	99
		3	-	-	790	96	101
		6	803	97	759	92	97

[redacted] ENGLAND

Document

Product:

HIGH POTENCY FACTORATE
(GENERATION IIB)
HEAT-TREATMENT

STABILITY REPORT

Number	Date
	MAY 1983

Replaces

2. POTENCY 3-HOUR POST RECONSTITUTION

BATCH NO.	STORAGE TEMPERATURE (°C)	TESTING INTERVAL (MONTHS)	UNHEATED CONTROL IU/VIAL	HEATED MATERIAL POTENCY	
				U/VIAL	% OF INITIAL HEATED
V 44106	2 - 8°C	0	-	783	100
		1	-	794	101
		2	-	781	100
		3	-	760	97
		6	-	755	96
		12	776	750	96
	15 - 30°C	0	-	783	100
		1	-	783	100
		2	-	777	99
		3	-	769	98
		6	-	765	98
		12	774	740	95
	35°C	0	-	783	100
		1	-	788	101
		2	-	772	99
		3	-	772	99
		6	812	765	96

oduct:

HIGH POTENCY FACTORATE
(GENERATION IIB)
HEAT-TREATED

STABILITY REPORT 36

Number

Date
MAY 1983

Replaces

2. POTENCY 3-HOUR POST RECONSTITUTION (Cont.)

BATCH NO.	STORAGE TEMPERATURE (°C)	TESTING INTERVAL (MONTHS)	UNHEATED CONTROL IU/VIAL	HEATED MATERIAL POTENCY	
				U/VIAL	% OF INITIAL HEATED
28602	2 - 8°C	0	-	797	100
		1	-	795	100
		2	-	887	99
		3	-	791	99
		6	-	885	97
		12	852	819	86
	15 - 30°C	0	-	797	100
		1	-	791	99
		2	-	876	96
		3	-	879	96
		6	-	876	96
		12	829	829	89
	36°C	0	-	797	100
		1	-	822	102
		2	-	791	99
		3	-	884	97
		6	700	858	93

3. SOLUTION TIME/APPEARANCE

BATCH NO.	STORAGE TEMPERATURE (°C)	TESTING INTERVAL (MONTHS)	UNHEATED CONTROL		HEATED MATERIAL	
			SOLUTION TIME	APPEARANCE	SOLUTION TIME	APPEARANCE
V 44106	2 - 8°C	0	22m 52s	Satisfactory	<16m	Satisfactory
		1	-	-	<16m	Satisfactory
		2	-	-	<13m	Satisfactory
		3	-	-	<14m	Satisfactory
		6	-	-	<16m	Satisfactory
		12	<12m	Satisfactory	<10m	Satisfactory
	15 - 30°C	0	22m 52s	Satisfactory	<16m	Satisfactory
		1	-	-	<10m	Satisfactory
		2	-	-	<10m	Satisfactory
		3	-	-	<14m	Satisfactory
		6	-	-	<11m	Satisfactory
		12	<6m	Satisfactory	<11m	Satisfactory
	35°C	0	22m 52s	Satisfactory	<16m	Satisfactory
		1	-	-	<14m	Satisfactory
		2	-	-	<13m	Satisfactory
		3	-	-	<12m	Satisfactory
		6	<17m	Satisfactory	<10m	Satisfactory

3. SOLUTION TIME/APPEARANCE (Cont.)

BATCH NO.	STORAGE TEMPERATURE (°C)	TESTING INTERVAL (MONTHS)	UNHEATED CONTROL		HEATED MATERIAL	
			SOLUTION TIME	APPEARANCE	SOLUTION TIME	APPEARANCE
V 28602	2 - 8°C	0	10m	Satisfactory	<10m	Satisfactory
		1	-	-	<13m	Satisfactory
		2	-	-	<10m	Satisfactory
		3	-	-	< 8m	Satisfactory
		6	-	-	< 8m	Satisfactory
		12	<8m	Satisfactory	< 8m	Satisfactory
	15 - 30°C	0	10m	atisfactory	<10m	Satisfactory
		1	-	-	< 7m	Satisfactory
		2	-	-	<10m	Satisfactory
		3	-	-	<10m	Satisfactory
		6	-	-	< 6m	Satisfactory
		12	<6m	Satisfactory	< 8m	Satisfactory
	35°C	0	10m	Satisfactory	<10m	Satisfactory
		1	-	-	<11m	Satisfactory
		2	-	-	< 8m	Satisfactory
		3	-	-	< 8m	Satisfactory
		6	<10m	Satisfactory	< 7m	Satisfactory

duct:

STABILITY REPORT

HIGH POTENCY FACTORATE
(GENERATION IIB)
HEAT-TREATED

Number	Date
	MAY 1983

Replaces

Stability data are presented for two batches of High Potency Factorate, which have been subjected to heat-treatment at 60°C for thirty-hours. The latter treatment has been shown to have possible beneficial effects in the prevention of transmission of non-A, non-B hepatitis virus which is thought to be heat labile.

BATCHES EXAMINED

The following normal production batches were subjected to heat-treatment. Experimental codes for these batches are included in parentheses.

V 28602 (A 1607-024)

V 44186 (A 1607-029)

TREATMENT

Vials of finished product have been subjected to heat treatment at 60°C (water-bath) for 30 hours and stored at refrigerated (2 - 8°C), room temperature (15 - 30°C) and elevated temperature (35°C) for the times specified in the results section.

RESULTS

After the specified storage periods, vials of finished product have been tested for potency, potency 3 hours after reconstitution, solution time and appearance. Potency values are expressed as units per vial and also as percentages of initial control (unheated) potency and initial potency of heated material to give information on the respective effects of heat-treatment and storage on the stability of the heat-treated product.

MEDICAL ASSESSMENT

Introduction

This is an abridged application for a Product Licence for a heat-treated version of Armour's High Potency Factorate. The untreated High Potency Factorate was licensed in 1979 and has been available since then.

The proposed uses for the heat-treated product are:

"Treatment of classical haemophilia A"

and the only additional claims to be made for it are the insertion of the following under "Further information":

"Experimental studies have shown that heat-treatment of Anti-Haemophilic Fraction may remove or reduce the risk of transmission of non-A non-B hepatitis. Consequently this product has been subjected to heat-treatment procedures during manufacture."

Apart from the heat-treatment applied to the vials of lyophilised product, the method of manufacture is said to be identical with that used for the untreated licensed product.

Pharmacy Points

The Chemistry and Pharmacy has of course been dealt with in detail by the Pharmaceutical Assessor but the following points should be noted:

1. There seems to be little information on how the temperature and duration of the heat-treatment were arrived at. A temperature of 60° for 30 hrs is used and there is a statement that 60° for 24 hrs was inadequate but the reasons for choosing these values and excluding others are not given.

2. The aluminium levels in the Finished Product Specifications are rather high. These are as follows:

u/vial	Al/vial	Al/l	Al/unit
250	10 ml< 50 mcg	5,000 mcg	0.2 mcg
500	20 ml<100 mcg	5,000 mcg	0.2 mcg
1,000	30 ml<180 mcg	6,000 mcg	0.18 mcg
2,000	60 ml<300 mcg	5,000 mcg	0.15 mcg

These values exceed the rule of thumb levels of 1,000 mcg Al/l and 0.1 mcg Al/u but it should be pointed out that the single batch analysis presented, for a 500 u vial, quotes<2 mcg/vial against a FPS of<100 mcg/vial. This would suggest that the company could tighten up the specification for aluminium without too much difficulty.

3. Further to 2., it is strange that the company have not presented batch analyses for each of the four strengths.

Experimental and Biological Studies

The company have presented three reports in this section:

1. A half-life study in haemophiliac dogs.
2. A blood pressure study in anaesthetised dogs.
3. A hepatitis transmission study in chimpanzees.

1. Half-life and recovery of heated and unheated antihemophilic Factor VIII in hemophilic dogs

Three haemophiliac dogs were given doses of 770 u FVIII by i.v. infusion. Two received heat-treated material, the other, untreated. A fourth dog, not included in the report but mentioned in the discussion, was given untreated FVIII and had a severe anaphylactoid reaction.

The numbers are too small to draw firm conclusions but the results indicate that heat-treatment does not reduce recovery or shorten half-life. In fact, the control dog had a recovery of 65% compared with 81% and 97% respectively for heat-treated material. The half-life in the control dog was 8 hours compared with 18 and 22 hours. Both products appeared well tolerated apart from the reaction described above.

2. Effects of antihemophilic factorate, heated and non-heated, on heart rate and mean arterial blood pressure in anesthetized dogs

Eight male beagles were anaesthetised and given either heat-treated or untreated FVIII by i.v. infusion. Heart rate and BP were monitored. Neither product appears to have produced any significant consistent change.

3. The in vivo infectivity assay of heat-treated antihemophilic factor containing non-A, non-B hepatitis virus (Hutchinson strain)

Previous work by the company had convinced them that heat-treatment of FVIII did not prevent the transmission of hepatitis B. Three chimpanzees had been given FVIII spiked with HBV; two had material which had been heat-treated after spiking while the third had untreated, spiked material. All three developed hepatitis B. However, it is suggested that "... the positive control animal had two courses of disease, the first of which was concluded due to non-A, non-B agent, presumed for this reason to be present in the test substance".

The study described employed five chimpanzees who were given FVIII spiked with Hutchinson strain non-A non-B virus. Three received material heat-treated after spiking and two received untreated, spiked material. One of the control animals developed NANBH but the other did not, even after re-challenge with unheated material. None of the three who had heat-treated material developed NANBH. Two were subsequently re-challenged with untreated material and developed NANBH.

Toxicology

The company state:

"Classical toxicological studies in animals have not been conducted with Factorate as such studies have been deemed inappropriate in view of the human origin of the material. Each batch of material produced is subjected to abnormal toxicity testing in mice and guinea pig and compliance with these tests is a requirement of the Finished Product Specification.

No further toxicological testing has been conducted with the heated material."

Studies in Humans

The only evidence presented in this section derives from "... a half-life study carried out in haemophiliac patients in the USA using a heat-treated preparation of Factorate (0231/0038) to which a small quantity of Hepatitis B Immune Serum Globulin has been added in processing."

The company are currently conducting a British clinical trial of their heat-treated product in "virgin" haemophiliacs under CTX 0231/0070A but no results have been submitted. Reference is made to the difficulty and slowness of such studies. The summary of this section is attached as APPENDIX A.

Although the clinical trial used material different from the subject of this application, the results are presented in great detail. They indicate that the heat-treated FVIII to which HB immune globulin was added was equivalent in terms of half-life, recovery and tolerance, to untreated material without the HB immune globulin.

MEDICAL COMMENT

1. The evidence submitted in support of this application is rather insubstantial.

2. Loss of potency caused by the heat-treatment is dealt with as part of the stability data and is difficult to quantify.

3. Reasons for choosing 60°C for 30 hours rather than other temperatures or times are not given.

4. The small amount of experimental data indicates that the half-life and recovery of the heat-treated material are comparable with the untreated licensed product but one would have expected more data from patients.

5. Tolerance appears comparable to that of the untreated licensed product but there is too little evidence to draw any firm conclusions.

6. There are no clinical data relating to the product for which the licence is sought.

7. There is evidence from the chimpanzee studies that heat-treatment may reduce the risk of transmission of non-A non-B hepatitis but the numbers

are very small and there are no clinical data to support this claim. The company clearly recognise this as shown by the statement at the end of their summary (Appendix A):

"Consequently the effectiveness of heat-treatment in reducing NANBV transmission may only become apparent epidemiologically and thus no strong claim is proposed for the effectiveness of this procedure at this time".

The claim made by the company is contained in the short paragraph intended for inclusion in the Data Sheet, which may be seen in the introductory section of this Medical Assessment.

8. In spite of the difficulties referred to by the company, it would not seem unreasonable to expect some clinical data from the CTX which they hold to form part of this application.

PART IV STUDIES IN HUMANS

Studies in humans have not been carried out specifically with Heat-treated High Potency Factorate; however the efficacy of High Potency factorate in replacing deficient levels of factor VIII in haemophiliacs is well-established.

Support for the hypothesis that the heat-treatment process is provided by the in vitro studies and biological studies in dogs and chimpanzees, reported in this application. In addition further supportive evidence is provided by a half-life study carried out in haemophiliac patients in the USA using a heat-treated preparation of Factorate (0231/0038) to which a small quantity of Hepatitis B Immune Serum Globulin has been added in processing. The study was carried out as an open two-way cross-over study in six haemophiliac patients. Extensive laboratory testing was carried out on blood samples collected at 0, 15, 30 and 60 minutes and 2, 4, 6, 8, 24 and 48 hours after infusion of test materials.

There were no significant differences in parameters measured, attributable to the heat-treatment process. Half-life and recovery values for the two materials were comparable and no adverse reactions or intolerance reactions to infusion of either material were encountered. A copy of the report of this study is attached.

The effectiveness of heat-treatment of Factorate products in reducing the risk of NANBV cannot readily be determined by clinical study. The incidence of NANBV in normal therapy is such that haemophiliac patients invariably contract the disease albeit in a mild form very soon after exposure to therapy. Thus in order to clearly demonstrate benefit it is necessary to rigidly exclude such patients from the study and rely on the recruitment of new 'virgin' patients who have not previously received treatment. Such patients are rare and their rate of recruitment too slow to provide meaningful results on a short-term basis. Such a study is currently in progress with Factorate under CTX 0231/0070A.

Consequently the effectiveness of heat-treatment in reducing NANBV transmission may only become apparent epidermiologically and thus no strong claim is proposed for the effectiveness of this procedure at this time.

Number:

PL 0231/0072

Company:

Armour Pharmaceutical Co Ltd

Product:

Heat-treated High-Potency Factorate

Therapeutic Class:

Anti-haemophilic Blood Product

Active Constituents:

Human Factor VIII

COMMITTEE ON SAFETY OF MEDICINES

SUB-COMMITTEE ON BIOLOGICALS

Draft Medical Recommendation

On the evidence before them, the Sub-Committee recommended that on grounds of safety and efficacy a Product Licence should be refused for this preparation.

The Sub-Committee considered that:

1. There was insufficient evidence of safety in clinical use.

2. There was insufficient evidence of efficacy in clinical use.

3. There was no clinical evidence relating to any changes brought about by the heat-treatment particularly in relation to the transmission of hepatitis.