DHSS

Armour Pharmaceutical Company Limited

St. Leonards House, St. Leonards Road, Eastbourne, Sussex BN21 3YG
Telephone: Eastbourne (0323) 21422 Telex: 87141

SJH/JJ

11th May, 1984

Department of Health and Social Security,
Medicines Division,
The Registration Section,
Room 1019-20,
Market Towers,
1 Nine Elms Lane,
Vauxhall,
LONDON,
SW8 5NQ

Dear Sirs,

HIGH POTENCY FACTORATE - PL 0231/0044

Thank you for your letter of 7th March, 1984, we will be requiring a Product Licence after the expiry date and we therefore enclose three copies of a completed MLA 231.

Thank you for your attention to this matter.

Yours faithfully,
ARMOUR PHARMACEUTICAL COMPANY LTD.

GRO-C

S. J. HINCE
Assistant Regulatory Affairs Manager

MEDICINES ACTS 1968 AND 1971

APPLICATION FOR RENEWAL OF PRODUCT LICENCE

A. Full name and address of licence holder: Armour Pharmaceutical Company Ltd., St. Leonards House, St. Leonards Road, Eastbourne, East Sussex, BN21 3YG

B. Particulars of Present Licence:

(i) Number: PL 0231/0044
(ii) Name of Product: High Potency Factorate
(iii) Date Granted: 13th June, 1979
(iv) Date of Expiry: 13th June, 1984

C. a) Dates of approval of changes in the original particulars: 14.10.80, 18.8.81, 6.4.82, 15.7.82, 6.4.84, 15.8.83, 31.7.80, 16.4.80

b) Dates of applications for change not yet determined:

D. If any further documents are attached, give number of pages and a brief description:

E. I/We apply for the renewal of the product licence described above for a period of five years from the date of expiry given above. The licence as renewed shall be in accordance with the particulars given above and on any accompanying documents, and those given in the original application as amended by the letters referred to in C above. The licence shall further be subject to all the provisions of the existing licence as now in force.

Date: 10.5.84 Signature: GRO-C
State capacity in which signed.
Assistant Regulatory Affairs Manager

Signature The form should be signed by the holder of the present licence. Where the licence is held by a company, the person signing should indicate in what capacity he does so (eg company secretary, director etc).

Name and address for communications: (if different from above)

(Official use only)

A 1

Form MLA 231

PRODUCT PARTICULARS - a complete set of pages should be included for each strength of product.

1. Number of Product:

PL 0231/0044

Name of Product and Strength: HIGH POTENCY FACTORATE

(Official use only)

2. Description of Pharmaceutical form (eg tablets, slow-release tablets, capsules etc):
Lyophilised cake in a vial with vacuum for intravenous administration to human beings after reconstitution.

(Official use only)

(Official use only)

3a. Legal status (place tick in appropriate box(es)) (Offical use only)

Prescription	X	Pharmacy		General Sales	

3b. Method of retail sale or supply:
FOR HOSPITAL SUPPLY ONLY.

(Official use only)

Text should be completed in block capitals

(Official use only)

D 1

4. Active Constituents:

(Official use only)	Name	Specification Reference	Quantity/Dose Unit or % quantity	Unit
	Dried Human Antihaemophilic Fraction	B P	250.	iu
			500.	iu
			1000.	iu
			2000.	iu
			.	
			.	
			.	
			.	
			.	
			.	
			.	
			.	
			.	
			.	

1. Please enter constituent as actual substance included in the formulation, eg. as salt not base where applicable.
2) Where a specification reference does not refer to the latest published monograph, the relevant year should be included in the Name column and not in the Specification Reference column. Where an ingredient has no official monograph please enter HSE in the Specification Reference column.
3) Where quantity is expressed as a percentage please insert WW, WV, etc. as appropriate in unit column. Please do not include percentage sign.
4) Trailing zeros following the decimal point may be omitted eg 10.02 MG will suffice.
5) Please photocopy page if more space for constituents is required.

(Official use only)

C	1																

5. Recommended clinical indications and route(s) of administration:

Indications

For use in therapy of classical haemophilia.

Route of Administration

Intravenous.

(Official use only)

All entries must be made in full. Cross references, eg. to accompanying data sheets are not acceptable. If a product is supplied under a generic name for prescription purposes and 1) a data sheet is not required to be held and 2) it is not advertised or supplied direct to the public, then the entry against item 5 should read eg "as in BP", and 6 should read "as directed by a Medical Practitioner". No entry need be made against item 8.

(Official use only)

B 1

6. **Recommended doses and dosage schedules:**

Distinguish between adults, children and the elderly and between different clinical indications

(Official use only)

(a) Standard Dose

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 of 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 fo he first 24 hours and the same dose every 12 hours for 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 at 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.

(Official use only)

7. **Name(s) of manufacturer(s) of the dosage form and site(s) of manufacture:**

Armour Pharmaceutical Company,
P.O. Box 511,
Kankakee,
Illinois 60901,
U.S.A.

B 1 (Official use only)

6. Recommended doses and dosage schedules:

Distinguish between adults, children and the elderly and between different clinical indications

(Official use only)

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.

(Official use only)

7. Name(s) of manufacturer(s) of the dosage form and site(s) of manufacture:

B 1 (Official use only)

6. Recommended doses and dosage schedules:

Distinguish between adults, children and the elderly and between different clinical indications

(Official use only)

(b) Children

It was demonstrated in a study using 8 month to 14 year old boys that 1 unit of AHF per kg body weight consistently produced an increase of 2% (of normal), which is of the same magnitude as in adults.

(c) Other Special Groups

Patients with inhibitors to Factor VIII receiving treatment with HIGH POTENCY FACTORATE may require doses in excess of those usually recommended for specific types of haemorrhage and/or bleed.

(d) Administration

HIGH POTENCY FACTORATE is for intravenous administration only and should be reconstituted using Water for Injections B.P. as recommended under Dilution (see Pharmaceutical Particulars) using standard aseptic precautions.

Standard aseptic techniques should be used at all times.

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.

(Official use only)

7. Name(s) of manufacturer(s) of the dosage form and site(s) of manufacture:

B 1 (Official use only)

6. **Recommended doses and dosage schedules:**

Distinguish between adults, children and the elderly and between different clinical indications

(Official use only)

1. Attach a filter needle to a sterile disposable syringe. Insert filter needle into stopper of HIGH POTENCY FACTORATE 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/minute.

(e) 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 Dilution.
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.

(Official use only)

7. **Name(s) of manufacturer(s) of the dosage form and site(s) of manufacture:**

B 1 (Official use only)

6. Recommended doses and dosage schedules:

Distinguish between adults, children and the elderly and between different clinical indications

(Official use only)

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.

(Official use only)

7. Name(s) of manufacturer(s) of the dosage form and site(s) of manufacture:

(Official use only)

B 1

8. **Contraindications, Precautions and Warnings:**

USE IN PREGNANCY

As the disease occurs almost exclusively in males, the eventuality of a pregnant woman requiring treatment with Factor VIII is extremely rare. There is, therefore, very little experience of the use of Factor VIII in pregnant women. Consequently, there is no evidence either in human pregnancy or in animal work that administration of Factor VIII is free from hazard.

CONTRAINDICATIONS

There are no knowncontraindications to antihaemophilic fraction.

PRECAUTIONS

ctor VIII contains low levels of group A and B isohaemaglutinins. 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.

WARNINGS AND ADVERSE EFFECTS

Factor VIII is prepared from human plasma, each donation of which has been found negative for hepatitis B surface antigen (BHsAg) 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 to patients is still present, and personnel administering and handling this material should also exercise appropriate caution.

Products of this type are known to cause mild chills, nausea or stinging at the infusion site. The possibility of allergic reactions occurring with the use of AHF concentrates cannot be discounted.

(Official use only)

B 1 (Official use only)

8. Contraindications, Precautions and Warnings:

TOXICITY AND TREATMENT OF OVERDOSE

Dosages of up to 150 iu/kg Factor VIII have been given 2 - 3 times daily in cases of acute bleeding episodes and 3 - 7 times a week during regular prophylactic treatment to remove inhibitors, with no untoward reactions reported. Such doses have been used for up to 7 months.

However, patients receiving very large amounts of therapeutic material may show signs of intravascular haemolysis and decreasing haematocrit values (see Precautions) as a result of haemaglutinins contained in the preparation. Haemolytic anaemia when present may be corrected by the administration of compatible Group O Human Red Blood Cells. Corrective therapy may also include the use of type specific cryoprecipitate as an alternative source of AHF.

(Official use only)

E 1 (Official use only)

9. Other constituents:

(Official use only)	Name	Specification Reference	mod	Quantity/Dose Unit or % quantity	Unit
	GLYCINE	U S P	Q S		
	SODIUM CITRATE	U S P	Q S		
	SODIUM CHLORIDE	U S P	Q S		
	SODIUM HEPARIN INJECTION	U S P	Q S		

1) Please leave a line between different components of the dosage form, eg. for capsule shell components, coating components.
2) Where a specification reference does not refer to the latest published monograph, the relevant year should be included in the Name column and not in the Specification Reference column. Where an ingredient has no official monograph please enter HSE in the Specification Reference column.
3) Please complete modifier column marked mod. as follows:
   Insert TO if final volume cannot be expressed as a complete quantity.
   Insert ND for substances not detectable in the final formulation, eg. solvents.
   Insert QS if quantity not fixed, eg. for substances used to adjust pH.
4) Where quantity is expressed as a percentage please insert WW, WV, etc. as appropriate in unit column. Please do not include percentage sign.
5) Trailing zeros following the decimal point may be omitted eg 10.02 MG will suffice.
6) Please photocopy page if more space for constituents is required.

(Official use only)

H | 1

10. Description of essential processes in the manufacture:

A cryoprecipitate is isolated from thawed human plasma and is dissolved at 25°C ± 5°C in glycine-saline buffer containing nmt 3 units/ml Sodium Heparin USP. The pH is adjusted with 0.1N Acetic Acid and/or 0.5N sodium hydroxide and filtered. Impurities are adsorbed onto aluminium hydroxide sterile suspension, centrifuged at approximately 15°C and the preparation stabilised with Sodium Citrate USP and Sodium Chloride USP (both pyrogen-free). The solution is cooled to approximately 0°C and cold ethyl alcohol (95%) added to a concentration of approximately 7%. The precipitate is isolated at low temperature and suspended in citrate-saline-glycine buffer. The pH is adjusted to 7.0 ± 0.2 with 0.5M sodium hydroxide. This solution may be stored at -40°C or colder if required at this stage. Such frozen solutions are thawed at 34 ± 4°C and brought to final volume with buffer. The pH is adjusted to 5.6 ± 0.3 with 0.5 acetic acid at controlled room temperature (15-30°C) and the solution is cooled to 8°C ± 5°C for up to 2 hours. The resulting precipitate is separated and the supernatant clarified by membrane filtration and the pH adjusted to 7.2 ± 0.4 with 0.5 M sodium hydroxide.

The solution is membrane filtered and finally sterile filtered through bacterial retentive membrane filters (0.8 µ down to 0.22 µ) before filling into sterile, Type I glass vials. The filled vials are frozen, lyophilised under vacuum and sealed.

11. Finished Product Specification:

	250 iu/vial	500 iu/vial	1000 iu/vial	2000 iu/vial
DESCRIPTION	White to pale yellow lyophilised cake			
VIAL SIZE	30 ml	50 ml	50 ml	100 ml
MAMMALIAN PROTEIN	Human positive, Bovine, Ovine and Porcine negative			
POTENCY	NLT 200 iu/vial	NLT 400 iu/vial	NLT 800 iu/vial	NLT 1600 iu/vial
HEPARIN	NMT 10 iu/vial	NMT 20 iu/vial	NMT 30 iu/vial	NMT 50 iu/vial
TOTAL PROTEIN	NMT 150 mg/vial	NMT 300 mg/vial	NMT 600 mg/vial	NMT 1200 mg/vial
FIBRINOGEN	NMT 120 mg/vial	NMT 240 mg/vial	NMT 480 mg/vial	NMT 960 mg/vial
ALUMINIUM	NMT 50 µg/vial	NMT 100 µg/vial	NMT 180 µg/vial	NMT 300 µg/vial
MOISTURE	NMT 0.5% w/w	NMT 0.5% w/w	NMT 0.5% w/w	NMT 0.5% w/w
FREEDOM FROM ABNORMAL TOXICITY				
MOUSE	Passes Test	Passes Test	Passes Test	Passes Test
GUINEA PIG	Passes Test	Passes Test	Passes Test	Passes Test
PYROGENS	Passes Test	Passes Test	Passes Test	Passes Test
STERILITY	Passes Test	Passes Test	Passes Test	Passes Test
SOLUTION TIME	NMT 20 Minutes	NMT 20 Minutes	NMT 20 Minutes	NMT 20 Minutes
pH	6.8 - 7.4 reconstituted			
ISOAGLUTININS	Not more than 1:256 without predilution and typically less than 1:64 when tested against Anti-A and Anti-B			
SODIUM CITRATE	Not more than 200 mmol/l reconstituted Not more than 55 mmol/l reconstituted			
HEPATITIS Bs ANTIGEN	Negative	Negative	Negative	Negative

(Official use only)

G | 1 |

12. Assembler(s):
Armour Pharmaceutical Company Ltd.,
Hampden Park, Eastbourne,
East Sussex,
BN21 3YG

13. Arrangements for storage:
The finished product is stored at the premises of Armour Pharmaceutical Co. Ltd., Hampden Park, Eastbourne, East Sussex, BN21 3YG

14. Importer:

The product will be imported by the Licence holder.

15. List other countries of registration:
Presentations of Factorate in various strengths are available in a number of countries including Holland, Ireland and the USA.

16. Site and Arrangements for Quality Control:
Quality Control of the ingredients, in-process controls and testing of the finished product is carried out by Armour Pharmaceutical Company, Kankakee, U.S.A.
The Quality Assurance Manager, Armour Pharmaceutical Company Limited decides if any batch is suitable for marketing on the basis of a Certificate of Analysis.
The product is subject to NIBS & C batch release.

17. Type of container(s), pack size(s), shelf life and storage precautions:

CONTAINERS
Type 1 glass vials with 20 mm neck finish and grey butyl rubber lyophilisation stoppers.
Vials sizes are
[illegible] iu/vial - 30 ml
[illegible] iu/vial - 50 ml
1000 iu/vial - 50 ml
200 iu/vial - 100 ml

Factorate high potency may be supplied with vials containing an appropriate quantity of Water for Injections BP.

Shelf-life - 2 years when stored between 2-8°C.

Within this period it may be stored at a temperature not exceeding 30°C for 6 months.

Container Size	Unit	(Official use only)

Note: **Please tabulate data in space allowed.**
Where applicable enter unit as MG, GM, ML, LT for litre etc.
No entry is required in Unit box for solid dosage forms.
Where coded entry is ambiguous leave as text.