

# **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, SWB 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 Armour Pharmaceutical Company Ltd., of licence holder: 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 0 2 3 1 0 0 4 4
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		

Official se only)			eci ati ere	on		%	Uni	y/Do or ntity		Un	1
	Dried Human Antihaemophilic Fraction	В	Р		2	5	0			i	Ĺ
					5	0	0			i	ţ
					10	0	0			i	-
					20	0	0			i	
											Ī
									$\top$		
111									T		-
											-
111									+		
								-			
+++			-					+	+	-	
+++				-	-		-	+	+-	H	
											ĺ

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.

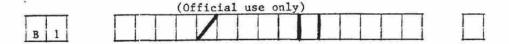
C 1	
	7
5. Recommended clinical indications and route(s) of administration:	
Indications	
For use in therapy of classical haemophilia.	İ
Route of Administration	
Intravenous.	
¥	
*	
(Official use only)	
L. L	

(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.

B 1
6. Recommended doses and dosage schedules:  Distinguish between adults, children and the elderly and between different clinical indications  (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%.
<ul> <li>Muscle Haemorrhages</li> <li>(a) Minor haemorrhages in extremities or non-vital areas: 10 units per kg once a day for 2 or 3 days.</li> <li>(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.</li> <li>(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.</li> <li>(Official use only)</li> </ul>
7. Name(s) of manufacturer(s) of the dosage form and site(s) of manufacture:  Armour Pharmaceutical Company, P.O. Box 511, Kankakee, Illinois 80901, U.S.A.

(Official use only)	Page 5
(Jilicial use only)	(Cont. 4)
B 1	
	<del></del>
6. Recommended doses and	
6. Recommended doses and dosage schedules:	
dosage schedules.	
Distinguish between adults, children and the	į.
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 so	lution.
5. After use, discard infusion set, needles and vials together with any unus	ed solution.
or most door disorder initiation soot moderate did visite vogether with dry dide	
	1
(Official use only)	1
	j
	1
7. Name(s) of manufacturer(s) of the dosage form and site(s) of manufacture	re:
	1
	i
	1
•	
	į
	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.

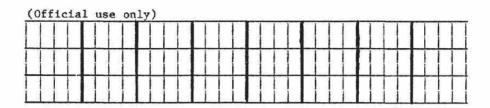
#### PRECAUTIONS

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 presonnel 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.



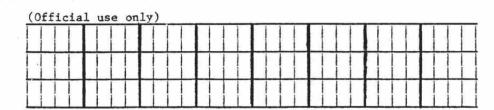
	(Officia	1 use onl	Ly)	
B 1				

# 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 us	se only)	
E 1			

9.	Other	constituents:													
	ficial only)	Name	F	ic	eci ati ere	on	m		Ouantity/Dose Unit or % quantity						
		GLYCINE		П	S	Р	Q	S			+				
		SODIUM CITRATE		IJ	S	Р	Ð	S							
		SODIUM CHLORIDE		U	S	Р	Q	S			+				
		SODIUM HEPARIN INJECTION		U	S	Р	Q	S			-				
											1	1			
											+				
											-				
											1		T		
										T	1				4
											1	$\top$			
									H	1	1	1			
											1	$\top$	1		
										1	+	+	+		
										+	1	$\top$	+		
11										+	1	$\top$	+		

- 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.

	 (Offi	cial use	only)	 
H 1				$\Box$

#### 10. Description of essential processes in the manufacture:

A cryoprecipitate is isolated from thawed human plasma and is dissolved at  $25^{\circ}\text{C} \pm 5^{\circ}\text{C}$  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  $15^{\circ}\text{C}$  and the preparation stabilised with Sodium Citrate USP and Sodium Chloride USP (both pyrogen-free). The solution is cooled to approximately  $0^{\circ}\text{C}$  and cold ethyl alcohol (95%) added to a concentration of approximately  $7^{\circ}$ . The precipitate is isolated at low temperature and suspended in citrate-saline-glycine buffer. The pH is adjusted to  $7.0 \pm 0.2$  with 0.5M sodium hydroxide. This solution may be stored at  $-40^{\circ}\text{C}$  or colder if required at this stage. Such frozen solutions are thawed at  $34 \pm 4^{\circ}\text{C}$  and brought to final volume with buffer. The pH is adjusted to  $5.6 \pm 0.3$  with 0.5 acetic acid at controlled room temperature ( $15-30^{\circ}\text{C}$ ) and the solution is cooled to  $8^{\circ}\text{C} \pm 5^{\circ}\text{C}$  for up to 2 hours. The resulting precipitate is separated and the supernatant clarified by rembrane filtration and the pH adjusted to  $7.2 \pm 0.4$  with 0.5 M sodium hydroxide.

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

11.	Finished	Product	Specifica	ition:
		250 .	/	_

	250 iu/vial	500 iu/vial	1000 iu/vial	2000 iu/vial
DESCRIPTION	White to pale yell	ow lyophilised cake		
VIAL SIZE	30 ml	50 ml	50 ml	100 ml
MAMMALIAN   PROTEIN	Human positive, Bo	vine, Ovine and Por	cine negative	
' "ENCY	NLT 200 iu/vial	NLT 400 iu/vial	NLT 800 iu/vial	NLT 1600 iu/vial
MLMARIN	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 ABN	IORMAL TOXICITY			
MOUSE	Passes Test	Passes Test	Passes Test	Passes Test
GUINEA PIG	Passes Test	Passes Test	Passes Test	Passes Test
	Passes Test	Passes Test	Passes Test	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 reconsti	tuted		
ISOAGLUTININS		56 without prediluti st Anti–A and Anti–E		ess than 1:64
SODIUM CITRATE		mmol/l reconstitut	(CO) (MR)	
HEPATITIS Bs ANTIGEN	Negative	Negative	Negative	Negative

/222	Page 9
G 1 (Official use only)	
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:  Proality Control of the ingredients, in-process controls and testing of the finished duct 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.  Container Size Unit use only) Vials sizes are 1 iu/vial - 30 ml 200 iu/vial - 50 ml 200 iu/vial - 100 ml	
Factorate high potency may be supplied wi vials containing an appropriate quantity 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 mor	nths.
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.	