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APPLICATION FOR VARIATION, AMENDMENT OR ADDITION TO INFORMATION SUPPLIED WITH PRODUCT AUTHORISATION APPLICATIONS

PA 10/6/1 - 3

April, 1987

Armour Pharmaceutical Company Limited
St Leonard's House
St Leonard's Road
Eastbourne
EAST SUSSEX
BN21 3YG

Form No PA

Application for Variation

Amendment or Addition to Information

Supplied with Product Authorisation Applications

Name of Product FACTORATE **PA Number** PA 10/6/1

Dose Form & Strength 50 ml vials each containing not less than 250, 500 or 1000 International Units of Dried Human Antihaemophilic Fraction.

Name and Address of Product Authorisation Holder ARMOUR PHARMACEUTICAL COMPANY LIMITED
ST. LEONARD'S HOUSE, ST. LEONARD'S ROAD
EASTBOURNE, EAST SUSSEX, BN21 3YG, ENGLAND.

. Amendment/Variation in details of Schedule to Authorisation. (Supportive evidence should accompany this application). (Statements should be given exactly as they appear in the schedule or as it is proposed that they appear).

PA Schedule Item No	Present Statement (see note below)	Proposed Statement
	Present Statement	Proposed Statement
B8	Labelling	Labelling
	The proprietary name.	The proprietary name and the words "Heat Treated".
B15	Precautions & Warnings	Precautions & Warnings
	1. At the present state of technical development it is not yet possible to exclude the possibility of transmission of virus hepatitis. 2. Because of the presence of quantities of A and B iso-haemagglutinins, administration of large volumes of the preparation to patients of blood group A, B or AB may lead to intravascular haemolysis.	Isolated cases of Acquired Immune Deficiency Syndrome (AIDS have been reported in haemophiliacs who have received blood and/or coagulation factor concentrates including Factor VIII concentrates. It is not known if the disease is due to a transmitted specific agent, the HIV virus, secondary to multiple antigenic exposures, or to some other mechanisms. The physician and patient should consider that Factor VIII concentrates may be associated with the transmission of AIDS and weigh the benefits of therapy accordingly.

Continued ...

Note:
1. Use separate sheet if space is insufficient for requirements.
2. Complete Schedule (attached) with final proposed amendment.

Application is hereby made for the above amendment to be made to the Authorisation.

Date . . . 8th April 1987 . . . . . Signature . GRO-C . . . . . .

Proposed Statement (Cont'd)

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 a haematocrit and direct Coombs test for signs of progressive anaemia.

. Variation or Additional Information (not requiring Amendment to Schedule) (Relevant documentation should accompany this application)

Subject Matter
(see itemised list)

Item 4 (d) - Method of Manufacture

Permission is requested to increase the terminal heat treatment of the final lyophilised product from 60°C for 30 hours to 68°C for 72 hours.

The accompanying documentation confirms that this increase in heat treatment does not adversely affect the structure, stability, safety, half-life or recovery of the Factor VIII. Neoantigens are not formed.

Index of Documents Accompanying this Application

See attached list.

Signature . . GRO-C . . . . . **Date** . . . 8th April 1987 . . . . . .

C. Office Use Only

Amendment/Variation/Addition No				
Date Received	Date Approved	Initial	Date of Issue to Department of Health	Date of Issue to Company

CHECKLIST

VARIATION (Amendment)

Item No	Item	Indicate
1.	Name (trading style) and address of Holder	
2.	Product Name	
3.	Drug Substance	
(a)	Source/Manufacturer	
(b)	Method of Manufacture	
(c)	Impurities	
(d)	Specifications	
(e)	Analytical Methods	
(f)	Other	
4.	Finished Dosage Form	
(a)	Product Form Description	
(b)	Formulation	
(c)	Manufacturer	
(d)	Method of Manufacture	X
(e)	Specifications	
(f)	Quality Control Procedures	
5.	Stability	
6.	Containers/Packaging	
7.	Labelling	X
8.	Shelf Life	
9.	Storage Precautions	
10.	Importer/Distributor	
11.	Method of Sale & Supply	

Item No	Item	Indicate
12.	Method of Promotion	
13.	Reconstitution	
14.	Incompatibilities	
15.	Other	
16.	Pharmacodynamic or Kinetic Characteristics	
17.	Clinical Use	
18.	Route of Administration	
19.	Dosage Instructions	
20.	Special Instructions for at risk categories	
21.	Contraindications	
22.	Precautions & Warnings	X
23.	Special Warnings	
24.	Significant side effects	
25.	Use during pregnancy and lactation	
26.	Interactions	

SCHEDULE

Endorsement No: . . . . . .

AMENDMENT TO PRODUCT AUTHORISATION

Product Authorisation No: PA 10/6/1 . . . . . .

Product Name: FACTORATE . . . . . .

Schedule Number & Heading	**Amended Statement**
B8 Labelling	Labelling The proprietary name and the words "Heat Treated". Precautions & Warnings Isolated cases of Acquired Immune Deficiency Syndrome (AIDS) have been reported in haemophiliacs who have received blood and/or coagulation Factor concentrates including Factor VIII concentrates. It is not known if the disease is due to a transmitted specific agent, the HIV virus, secondary to multiple antigenic exposures, or to some other mechanisms. The physician and patient should consider that Factor VIII concentrates may be associated with the transmission of AIDS and weigh the benefits of therapy accordingly. 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 a haematocrit and direct Coombs test for signs of progressive anaemia.

FACTORATE HEAT TREATED - DRIED HUMAN

ANTI-HAEMOPHILIC FRACTION

EXPERT REPORT - CLINICAL

The previous Product Authorisations PA 10/6/1, PA 10/6/2 and PA 10/6/3 described the preparation of a Dried Human Anti-haemophilic Fraction from pooled human plasma.

A variation to this licence of 13 February 1985 described the heating of the final lyophilised product at 60°C for 30 hours to reduce the risk of virus transmission.

Following reports of two haemophiliacs who sero-converted after receiving only the heat treated material for approximately 18 months, Factorate was withdrawn from the market and the licence surrendered.

The product which is the subject of this application is identical in all respects to the manufacturing process of that previously licensed except that the terminal heating of the final lyophilised product has been increased to 68°C for 72 hours.

A safety, half-life and recovery study has been conducted to ensure that the increased heating procedure has not affected the safety or clinical efficacy of the Factorate Heat Treated.

The study was an open, balanced two way crossover study conducted at a single centre. It compared Armour Factorate product, heat treated at 60°C for 30 hours with the revised heat treated Factorate, heat treated at 68°C for 72 hours in 6 haemophiliacs. Each patient's dose was based on the usual prophylactic dose and ranged from 25.3 to 51.2 u/kg for the 60°C 30 hour product and 23.6 to 48.3 u/kg for the 68°C 72 hour product.

Safety was determined by physical examination, adverse experiences and clinical laboratory tests. Half-life & recovery was performed for each product and a comparison made.

The half-life, after a single infusion of the 60°C 30 hour Heat Treated Factorate ranged between 13.5 and 32.7 hours (mean 21 hours $\pm$ 6.6). The half-life, after a single infusion of the 68°C 72 hour Heat Treated Factorate ranged between 13.4 and 21.7 hours (mean 17.6 hours $\pm$ 3.3). There was no statistically or clinically significant difference in half-life between these products. Individual kinetics graphs are attached.

Recoveries for the two products were also not statistically or clinically different, being a mean rise of 1.7 $\pm$ 0.7 u/kg for the 60°C 30 hours heated product and 1.6 $\pm$ 0.5 u/kg for the 68°C 72 hour heated Factorate.

Coagulation and serology determinations showed no clinically significant changes. While there were a few isolated clinical chemistry and haematology values outside the normal range, none were considered significant for haemophiliacs, and there were no clinically significant changes after infusion with either study medication.

A total of five adverse experiences were reported by two of the six patients. Two adverse experiences (headache and mental fuzziness) were considered possibly drug related due to the patient's history of similar reactions to any AHF concentrate. All other adverse experiences were mild, not serious and not related to the test medication.

It may be concluded that on the basis of this study there were no significant differences in half-life or recovery between Factorate heated at 60°C for 30 hours and the same product heated at 68°C for 72 hours. Both products were well tolerated, safe and effective in treating patients with Haemophilia A.

SIGNATURE ..... GRO-C .....

A. SCHREIBER, M.D.

DATE ..... 4/15/87 .....

PLACE ..... Springfield VA 22151

APPLICATION FOR VARIATION

AMENDMENT OR ADDITION TO INFORMATION

SUPPLIED WITH PRODUCT AUTHORISATION APPLICATIONS

FOR HEAT TREATED FACTORATE

CONTENTS PAGE NO

FACTORATE HEAT TREATED - DRIED HUMAN ANTI-HAEMOPHILIC FRACTION

EXPERT REPORT - CLINICAL

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A variation to this licence of 13 February 1985 described the heating of the final lyophilised product at 60°C for 30 hours to reduce the risk of virus transmission.

Following reports of two haemophiliacs who sero-converted after receiving only the heat treated material for approximately 18 months, Factorate was withdrawn from the market and the licence surrendered.

The product which is the subject of this application is identical in all respects to the manufacturing process of that previously licensed except that the terminal heating of the final lyophilised product has been increased to 68°C for 72 hours.

A safety, half-life and recovery study has been conducted to ensure that the increased heating procedure has not affected the safety or clinical efficacy of the Factorate Heat Treated.

The study was an open, balanced two way crossover study conducted at a single centre. It compared Armour Factorate product, heat treated at 60°C for 30 hours with the revised heat treated Factorate, heat treated at 68°C for 72 hours in 6 haemophiliacs. Each patient's dose was based on the usual prophylactic dose and ranged from 25.3 to 51.2 u/kg for the 60°C 30 hour product and 23.6 to 48.3 u/kg for the 68°C 72 hour product.

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The half-life, after a single infusion of the 60°C 30 hour Heat Treated Factorate ranged between 13.5 and 32.7 hours (mean 21 hours $\pm$ 6.6). The half-life, after a single infusion of the 68°C 72 hour Heat Treated Factorate ranged between 13.4 and 21.7 hours (mean 17.6 hours $\pm$ 3.3). There was no statistically or clinically significant difference in half-life between these products. Individual kinetics graphs are attached.

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It may be concluded that on the basis of this study there were no significant differences in half-life or recovery between Factorate heated at 60°C for 30 hours and the same product heated at 68°C for 72 hours. Both products were well tolerated, safe and effective in treating patients with Haemophilia A.

SIGNATURE ..... GRO-C .....

A. SCHREIBER, M.D.

DATE ..... 4/15/87 .....

PLACE ..... Springfield VA 22151

FACTORATE HEAT TREATED DRIED HUMAN ANTI-HAEMOPHILIC FRACTION

EXPERT REPORT - CHEMISTRY AND PHARMACY

The previous Product Authorisations PA 10/6/1, PA 10/6/2 and PA 10/6/3 described the preparation of a Dried Human Anti-haemophilic Fraction from pooled human plasma. The individual donations are tested for hepatitis B antigen and the human immunodeficiency virus antibody and found to be negative, and values within the normal range for alanine aminotransferase are found at screening. Plasma is stored frozen until required for processing.

Cryoprecipitate as collected from the thawed human plasma is dissolved in a buffer containing glycine, sodium chloride and heparin. Impurities such as prothrombin are adsorbed with aluminium hydroxide after which the preparation is stabilised with sodium citrate and heparin in an isotonic medium. Following the addition of stabilisers the solution is sterile filtered, filled into vials and lyophilised.

A Product Licence Variation of 13 February 1985 described the heating of the final lyophilised product at 60°C for 30 hours intended to reduce the risk of virus transmission.

Following reports of two haemophiliacs who sero-converted after receiving only the heat treated material for approximately 18 months, Factorate was withdrawn from the market and the Licence surrendered. The product which is the subject of this application is identical in all respects of the manufacturing process to that previously licensed but the terminal heating of the final lyophilised product has been increased to 68°C for 72 hours.

The tests to be described confirm that the increased heating process has achieved an increased inactivation of the Human Immunodeficiency Virus without significant deleterious effects on the structure or stability of the Factorate product.

1. Effect of Heating Lyophilised Factorate on Factor VIII C Activity

Vials of released lyophilised products were either refrigerated at 4°C (controls) or heated to 68°C for 72 hours. Controls and heated vials were reconstituted with sterile Water for Injection and assayed for Factor VIIIC activity. The appearance of the lyophilised cake, solution and reconstitution time were noted. The assays were repeated on the control and test vials 3 hours after reconstitution.

No discernible difference was detected between the control and heated samples with respect to any of the parameters tested.

This confirms that heating Factorate at 68°C for 72 hours did not alter the biological activity of the Factor VIII C or the physical properties of the vial contents compared to the unheated control preparations.

2. Immunological Analysis of Factor VIII Structure Comparing Heated and Unheated Factorate by the Western Blotting Techniques

Comparisons were made by the Western Blotting technique of three lots of Factorate (Generation I) by the direct application of heated and unheated samples. Heated samples were subjected to either 60°C for 30 hours or 68°C for 72 hours.

In other work difficulties had been encountered from the interference of other plasma proteins. This type of interference was reduced, but not completely eliminated, by the use of an optimum sample. To improve resolution and identification of those components inclusive of biologically active forms, preliminary immune absorption with solid phase derivatives of monoclonal antibodies C_2 and C_5 was adopted. Western blot separation of the eluates was then carried out as before.

The overall appearance of the primary transblots was similar in that the number and position of the bands was essentially the same.

In separate runs, the position of the Factor VIII peptides had been confirmed as consistent with the calibration number set used in the system.

It was not possible to interrelate the bands quantitatively by this analysis system.

It was concluded that the structural analysis of Factorate Generation I heated at 60°C for 30 hours and 68°C for 72 hours contained all the peptide forms of Factor VIII expected from the previous observations of other workers and do not differ from unheated materials of the same batch.

3. Neoantigen Study on Heat Treated Factorate (Generation I)

Two groups of rabbits were immunised with Factorate heated for 30 hours at 60°C, 60 hours at 60°C and 72 hours at 68°C. 5 ml of serum from the 28 day bleed of each rabbit were pooled and the IgG fractionated. Sera were pooled to reduce inter-animal differences in the intensity or specificity of response that could lead to confusion in the interpretation of results.

Two-dimensional electrophoresis was carried out to separate individual protein components. Gels in the second dimension contained antibodies to non-heated and heated Factor VIII. All peaks appeared in the gel containing antibodies to the unheated product. It was concluded that no new antibodies were generated against components of the heated Factorate samples.

4. Infectivity Assay of Factorate Intentionally Seeded with LAV/HTLV-III (Human Immunodeficiency Virus, H.I.V.)

Samples of Factorate (Generation I) were reconstituted with Water for Injection and seeded with a small quantity of highly concentrated and partially purified LAV (HIV) suspended in an albumin/saline buffer.

After freezing and lyophilisation in standard vials, the sample was sub-divided into four sections - Control, which was reserved for assay and the remaining three were heated under the following conditions:

1. 60°C for 30 hours
2. 60°C for 60 hours
3. 68°C for 72 hours

Samples submitted for viral assay included an aliquot of the infected product that had not been lyophilised so that the effect of freeze drying could be assessed.

The virus was assayed by the production of cytophathology in CEM suspension cultures.

The results obtained are shown in the following table:

Sample		$\log_{10}$ ID 50/ml	$\log_{10}$ reduction
AHF + LAV (HIV) frozen		$\geq$ 7.8	-
lyophilised		5.3	> 2.5
Heated	60°C 30 hours	$\geq$ 2.8	< 5.0
	60°C 60 hours	$\geq$ 2.8	$\leq$ 5.0
	68°C 72 hours	0.4	$\geq$ 7.4

The experiment showed a reduction of the HIV virus by lyophilisation of > 2.5 logs. Heating at 68°C for 72 hours led to a further reduction of 4.9 $\log_{10}$ ID_{50} ml of product. In this study, this is a total of $\geq$ 7.4 $\log_{10}$ ID_{50}/ml. Heating at 60°C for 30 or 60 hours led to a substantially lower reduction of virus being a total of 5.0 $\log_{10}$ ID_{50}/ml.

5. Product Stability

Stability tests have been conducted on three batches of Heat Treated Factorate which have been subjected to heat treatment at 68°C for 72 hours.

Tests were conducted over a three month period at 5° and 37°C. No significant loss of potency was observed during this period at either temperature.

Three hour post-reconstitution potency was also checked initially and after 3 months storage at 5°C. 100% reconstitution potency was observed after 3 hours initially and after 3 months storage.

These stability tests are continuing with samples stored at 5°C and 25°C.

The results to date indicate excellent stability of the Factorate product heated at 68°C for 72 hours.

From the tests described above, it may be concluded that subjecting Factorate to a terminal heating process of 68°C for 72 hours as the only additional dsprocessing step induces no measurable alteration to the structure or stability of the product. Neoantigens are not produced by this process and there is a significant increase in the $\log_{10}$ reduction of an added HIV virus challenge compared to the product heated at 60°C for 30 hours.

SIGNED GRO-C .....

M. HRINDA

DATE April 15, 1987

PLACE Springfield Va, USA.

BACKGROUND AND QUALIFICATIONS

Alain B. Schreiber, M.D. - Vice President, Meloy Laboratories
Michael E. Hrinda, Ph.D. - Director of Development, Meloy Laboratories

Meloy Laboratories, Inc. is the wholly-owned biotechnology subsidiary of Rorer Central Research. Meloy's R&D efforts are focused in the areas of hemostasis, prevention and therapy of thrombotic disorders, antibodies as therapeutic agents and growth factors. Meloy is functionally divided into a research and a development division, supported by financial and administrative departments. With an established animal colony and manufacturing pilot plant, Meloy is able to validate product concepts from the exploratory stage through the production and release of clinical lots. Meloy is integrated within Rorer Central Research for additional drug development activities including toxicology, clinical trials and registration.

Meloy was founded in 1970 as a company providing biological services to the United States federal government. Thanks to its location, strong ties were established with NIH scientists. From 1975 to 1986, Meloy functioned as the Biotechnology Research Division of Revlon Health Care Group. During this period, Meloy had a successful interaction with Armour Pharmaceuticals, then a Division of Revlon Health Care Group. Meloy and Armour were acquired by Rorer in 1986, as part of the Rorer-Revlon Health Care merger. Close cooperation and interaction between Meloy, Armour Pharmaceuticals and its International companies, to develop and register new drugs, is continued in this new relationship.

Alain B. Schreiber, M.D., Vice President. Dr. Schreiber was trained at the Free University of Brussels, where he worked as research fellow in the Clinical Chemistry Department. During his training as immunohematologist, Dr. Schreiber demonstrated first that anti-idiotypic antibodies could function as internal images of beta-adrenergic ligands. He then spent a post-graduate period at the Weizman Institute in Israel. His work involved the generation of monoclonal antibodies to the EGF-receptor and the analysis of transmembrane signaling in this system. Dr. Schreiber subsequently joined Syntex Research, where he successively help positions of section leader and department head of Biochemistry. In these functions, he was responsible for programs on protease inhibitors, anti-angiogenic agents and lipoxygenase inhibitors. Research on growth factors, peptide antagonists and hormone receptors was performed in his department. Dr. Schreiber was also the coordinator of the joint venture between Syntex and Immunex on applications of recombinant interleukin-1. Dr. Schreiber joined Meloy in 1985.

Michael E. Hrinda, Ph.D., Director of Development. Dr. Hrinda was trained in biochemistry at the University of Chicago. From 1969 to 1980, he held successively positions of increasing management importance at Armour Pharmaceutical Company in process development and protein biochemistry. Dr. Hrinda contributed to the development of many of the products currently marketed by Armour Pharmaceuticals, including the various human serum albumin preparations and anti-hemophilic factor products. From 1980 to 1985 Dr. Hrinda continued work on the development of plasma protein therapeutics in collaboration with Armour as Director of Protein Biochemistry of Revlon Health Care Central Research. He joined Meloy Laboratories in 1985. In these capacities he has managed R&D activities in drug development and testing, and has provided numerous reports supporting drug registrations in both the U.S. and international forums.

PART II: CHEMICAL AND PHARMACEUTICAL DOCUMENTATION

PART IIA: COMPOSITION

The containers are as described in PPA 10/6/1 - 3.

The composition of the product after reconstitution with the recommended quantity of diluent is as follows:

	CONC. IN RECON. PROD.	WT. 250 U/V	Range	WT. 500 U/V	Range	WT. 1000 U/V	Range	CONC. QUOTED IN PL0231/0038
Glycine	Approx. 0.06M	45 mg	22.5 - 62.5 mg	90 mg	45 - 125 mg	180 mg	90 - 250 mg	0.02M
Sodium Chloride	Approx. 0.07M	40 mg	22.5 - 57.5 mg	80 mg	44 - 115 mg	160 mg	90 - 230 mg	0.04M
Sodium Citrate	Approx. 0.015M	44 mg	20 - 55mg	88 mg	40 - 110 mg	176 mg	80 - 220 mg	0.04M
Heparin	Max. 1.25 iu/ml		-		-		-	NMT 2.5 u/vial

The revised composition quoted does not reflect a product change but an arithmetical error in the original registered product details, which we wish to correct as part of this application.

Development Pharmaceutics

A number of new studies have been carried out on the product heated at 68°C for 72 hours; these are described below.

1. Analytical Control

The analytical control procedures applied to this product are identical to those already described in PA 10/6/1 - 3.

2. Effect of Heat Treatment on Factor VIII Structure

An experimental study was carried out to compare heat treated and unheated Factorate by Western Blot immunological analysis, a procedure which compares Factor VIII molecular species in the two products.

For these batches of product, the structural analysis of samples heated at 60°C for 30 and 60 hours, and at 68°C for 72 hours contained all the peptide forms of Factor VIII expected from previous observations and did not differ from unheated controls.

A copy of the report on this study is presented in the Appendix to this file (1).

3. Effect of Heat Treatment on Factor VIII:C Activity

Vials of Factorate heat treated at 68°C for 72 hours, were compared with unheated controls using the 2-stage asay (GOP 36/1981).

Results showed that the heating process did not alter the biological activity of Factor VIII:C or the physical properties of the vial contents from those of unheated control preparations.

Comparison of Factor VIII:C Activity
68°C for 72 hours v unheated control

Batch		Factor VIII:C Activity Reconstituted	Units/Vial After 3 hours at RT
A43610	Control	560	550
	Heated	582	592
598	Control	814	-
	Heated	806	-
604	Control	232	-
	Heated	257	-
608	Control	1236	-
	Heated	1311	-

A copy of the report on this study is presented in the Appendix to this file (2).

4. Effect of Heat Treatment on Quantitative Reduction of LAV/HTLV-III VIRUS

Samples of Factorate were intentionally seeded with LAV/HTLV-III (HIV) virus prior to lyophilisation and subjected to heat treatment at 60°C for 30 hours, 60°C for 60 hours and 68°C for 72 hours.

Results showed that the virus was inactivated by lyophilisation, with a further reduction in numbers of heating at 68°C for 72 hours.

Sample	Log_{10} 50% Infections doses per ml	Log_{10} Reductions
AHF + LAV (HIV) Frozen	>7.8	-
Lyophilised	5.3	>2.5
Heated 60°C/30 hours	>2.8	<5.0
Heated 60°C/60 hours	>2.8	<5.0
Heated 68°C/72 hours	0.4	7.4

A copy of the report on this study is presented in the Appendix to this file (3).

5. Neoantigen Study with Heat Treated Product

In this study, groups of rabbits were immunised with Factorate heated for 30 hours at 60°C, 60 hours at 60°C and 72 hours at 68°C.

The IgG fraction was isolated from the hyperimmune sera and analysed for antibodies against neoantigens by a highly specific 2-dimensional immunoelectrophoresis with an intermediate reference gel. By this procedure, no neoantigens could be demonstrated in any of the heat treated samples.

A copy of the report on this study is presented in the Appendix to this file (4).

Conclusion

It is concluded that the increase in heat treatment from 60°C for 30 hours to 68°C for 72 hours as the only altered manufacturing process step does not significantly alter any essential feature of the product. There are no deleterious effects on the structure or stability of the Factorate but an increased inactivation of the HIV virus has been demonstrated.

PART IIB: METHOD OF PREPARATION

The product is manufactured and filled as previously described (PA 10/6/1 - 3), with the exception of the following step:

Heat Treatment

Lyophilised final containers are heated at 68°C for 72 hours.

PART IIC: CONTROL OF STARTING MATERIALS

Specifications for constituents are as previously described in PA 10/6/1 - 3.

PART IID: CONTROL TESTS ON INTERMEDIATE PRODUCTS

Not applicable.

PART IIE: CONTROL ON TESTS ON THE FINISHED PRODUCT

As previously described in PA 10/6/1 - 3, except for the following minor modifications:

(i) Moisture method 430 has been re-numbered 1561.

(ii) An alternative microtitre method (No. K/1426) has replaced method 386 for isoagglutinins.

Copies of these revised methods are included in the Appendix to this file (6).

PART IIF: STABILITY

A stability report providing data on the storage of new heat treated Factorate vials for up to 3 months at 5°C and 37°C is attached. All the batches continued to meet acceptance criteria for all parameters evaluated and it is proposed that the shelf life of the product should be 2 years. Studies are ongoing on these and two additional batches and the results will be forwarded to the DHSS as they become available.

ARMOUR PHARMACEUTICAL COMPANY LIMITED
EASTBOURNE ENGLAND

STABILITY REPORT

PRODUCT:	Number:	1
HEAT TREATED FACTORATE	Date:	March, 1987
	Replaces:	New

Stability data are presented for three batches of Heat Treated Factorate, which have been subjected to heat treatment at 68°C for 72 hours.

BATCHES EXAMINED

The following batches were examined:

B78206
B78306
B78406

TREATMENT

Vials of finished product were subjected to heat treatment at 68°C for 72 hours, and stored for 3 months at 5°C and 37°C.

CONTAINERS

Type 1 glass with Tompkins, PT 24-B0857, grey, butyl rubber closure.

PARAMETERS ASSESSED

AHF potency, AHF potency 3 hours after reconstitution (at RT), pH of reconstituted solution, appearance of the lyophilised cake, reconstitution time and moisture, according to the methods referenced in the tables of results.

RESULTS

All batches continued to meet acceptance criteria for all parameters evaluated after 3 months storage at 5°C or 3 months storage at 37°C.

ARMOUR PHARMACEUTICAL COMPANY LIMITED
EASTBOURNE ENGLAND

STABILITY REPORT

PRODUCT:

HEAT TREATED FACTORATE

Number: 1

Date: March, 1987

Replaces: New

1. POTENCY

BATCH	STORAGE TEMP	INTERVAL Months	POTENCY AHF Units/Vial (% of Initial)
B78206	5°C ± 3°C	0	1025 (100%)
		3	1025 (100%)
	37°C	0	1025 (100%)
		3	970 (95%)
B78306	5°C ± 3°C	0	1010 (100%)
		3	1055 (104%)
	37°C	0	1010 (100%)
		3	1000 (99%)
B78406	5°C ± 3°C	0	735 (100%)
		3	745 (101%)
	37°C	0	735 (100%)
		3	745 (101%)

Specification: 80 - 120% of Initial (Method No. 365)

ARMOUR PHARMACEUTICAL COMPANY LIMITED
EASTBOURNE ENGLAND

STABILITY REPORT

PRODUCT:	**Number:**	1
HEAT TREATED FACTORATE	**Date:**	March, 1987
	Replaces:	New

2. THREE-HOUR POST-RECONSTITUTION POTENCY

BATCH	STORAGE TEMP	INTERVAL Months	POTENCY AHR Units/Vial (% of Initial)
B78206	5°C ± 3°C	0	1025 (100%)
		3	1030 (100%)
	37°C	0	1025 (100%)
		3	Not tested
B78306	5°C ± 3°C	0	1010 (100%)
		3	1030 (102%)
	37°C	0	1010 (100%)
		3	Not tested
B78406	5°C ± 3°C	0	735 (100%)
		3	740 (101%)
	37°C	0	735 (100%)
		3	Not tested

Specification: 80 - 120% of Initial (Method No. 365)

ARMOUR PHARMACEUTICAL COMPANY LIMITED
EASTBOURNE ENGLAND

STABILITY REPORT

PRODUCT:	**Number:**	1
HEAT TREATED FACTORATE	**Date:**	March, 1987
	Replaces:	New

3. pH/SOLUTION TIME/APPEARANCE

BATCH	STORAGE TEMP	INTERVAL Months	pH	SOLUTION TIME Minutes	APPEARANCE
B78206	5° ± 3°C	0	7.4	1	Pass
		3	7.3	5	Pass
	37°C	0	7.4	1	Pass
		3	7.3	1	Pass
B78306	5° ± 3°C	0	7.4	3	Pass
		3	7.2	5	Pass
	37°C	0	7.4	3	Pass
		3	7.3	5	Pass
B78406	5° ± 3°C	0	7.5	2	Pass
		3	7.3	2	Pass
	37°C	0	7.5	2	Pass
		3	7.3	6	Pass

Specification:

pH 7.1 - 7.9 (Method No. 53)

Solution Time: Not more than 30 Minutes (Method No. 1079)

Appearance: Conforms to description (Method No. 1396)

For details of these methods see Appendix (7).

CONCLUSIONS

Heat Treated Factorate, heated for 72 hours at 68°C as final lyophilised product, displays excellent stability characteristics after storage for 3 months at 5°C or 3 months at 37°C.

Stability studies are continuing with samples stored at 5°C and 25°C.

PART III: TOXICOLOGICAL AND PHARMACOLOGICAL DOCUMENTATION

Full information on all studies is given in PA 10/6/1 - 3. No new studies have been carried out.

PART IV: CLINICAL DOCUMENTATION

PART IVA: HUMAN PHARMACOLOGY

Full information on all studies is given in PA 10/6/1 - 3. An additional study comparing the safety, half-life and recovery of material heated at 68°C for 72 hours with previously marketed Factorate is summarised below.

Type of Study

Open, balanced, two-way crossover study comparing previously marketed Factorate with Factorate heated at 68°C for 72 hours.

Number/Sex of Patients

6 home-care male patients with documented Haemophilia A.

Criteria for Exclusion

Alcohol or drug abuse, seizures, thrombocytopenia, chronic illness (other than hepatitis), use of aspirin, other bleeding disorders, circulating Factor VIII inhibitor.

Six patients received test medication; no withdrawals.

Daily Dosage/Duration

Single I.V. infusion of each preparation, separated by washout period of 48 hours. Units infused were 2170 - 3255 u (mean 2532 ± 560) for Factorate and 2050 - 3075 u (mean 23274 ± 526) for material heated at 68°C for 72 hours. Each patient received a comparable dose of either product.

Results

	Factorate (60°C/30 hours)	Factorate (68°C/72 hours)
Half-life	13.5 - 32.7 hours (Mean ± S.D. 21.1 ± 6.6)	13.4 - 21.7 hours (Mean 17.6 ± 3.3)
Recovery	1.0 - 2.9 u/dL msc/u/kg (Mean 1.7 ± 0.7)	0.9 - u/dL rise/u/kg (Mean 1.6 ± 0.5)

There was no statistically or clinically significant difference between the two products.

Coagulation ---------- Sera at 48 hours post-infusion had no Factor VIII inhibitors and prothrombin times were within normal limits (10.8 -12.3 sec).

Serology --------- Sera was +ve for HBs antibody and -ve for HBs antigen. Three patients had +ve Coombs test before and during the study, and in three patients sera was -ve throughout. No clinically significant changes.

Laboratory ---------- Determinations ----------

No clinically significant changes. The following were noted:

- SGOT levels elevated throughout study in 2 patients.
- 2 patients had platelet counts considerably below normal lower limit throughout.
- 2 patients had WBCs below 3900 cells/cu mm throughout.

Adverse Reactions

A total of 5 adverse reactions were reported by 2 patients (33%). Two (headache and mental fuzziness) were considered possibly drug related due to patient's history of similar reactions to any AHF concentrate. All other adverse experiences were mild, not serious and not drug related.

Conclusions

Comparisons of half-life and recovery between the two products showed no significant differences. The product heated at 60°C for 72 hours was well tolerated, safe and effective in treating patients with Haemophilia A.

A copy of the report on this study is presented in the Appendix to this file (5).

PART IVB: CLINICAL DOCUMENTATION

Full information on all studies is given in PA 10/6/1 - 3. See also PART IV A: HUMAN PHARMACOLOGY, page 18 of this application.

PART IVC: OTHER INFORMATION

Not applicable.

PART V: SPECIAL PARTICULARS

PART VA: DOSAGE FORM

Packaging is as previously described in PA 10/6/1 - 3.

Specimen Label Text, Package Insert and Data Sheet Text are presented in the Appendix to this file (8).

PART VB: SAMPLES

No samples accompany this application, but can be provided if required for assessment purposes.

PART VC: MANUFACTURERS AUTHORISATION(S)

As previously described in PA 10/6/1/ - 3.

PART VD: MARKETING AUTHORISATION(S)

Product is currently marketed in the United States of America and West Germany.

Applications are under consideration in Canada, Israel, Brazil and the Republic of Ireland.

An application for marketing has never been refused in any country.

Form No PA

Application for Variation

Amendment or Addition to Information

Supplied with Product Authorisation Applications

Name of Product FACTORATE (Double Fill) **PA Number** PA 10/6/2

Dose Form & Strength 100 ml vials, each containing a minimum of 225 International Units of Dried Human Antihaemophilic Fraction B.P.

Name and Address of Product Authorisation Holder

ARMOUR PHARMACEUTICAL COMPANY LIMITED
ST. LEONARD'S HOUSE, ST. LEONARD'S ROAD
EASTBOURNE, EAST SUSSEX, BN21 3YG
ENGLAND.

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1. Amendment/Variation in details of Schedule to Authorisation. (Supportive evidence should accompany this application). (Statements should be given exactly as they appear in the schedule or as it is proposed that they appear).

PA Schedule Item No	Present Statement (see note below)	Proposed Statement
	Present Statement	Proposed Statement
B8	Labelling The proprietary name.	Labelling The proprietary name and the words "Heat Treated".
B15	Precautions & Warnings 1. At the present state of technical development it is not yet possible to exclude the possibility of transmission of virus hepatitis. 2. Because of the presence of quantities of A and B iso-haemagglutinins, administration of large volumes of the preparation to patients of blood group A, B or AB may lead to intravascular haemolysis.	Precautions & Warnings Isolated cases of Acquired Immune Deficiency Syndrome (AIDS) have been reported in haemophiliacs who have received blood and/or coagulation factor concentrates including Factor VIII concentrates. It is not known if the disease is due to a transmitted specific agent, the HIV virus, secondary to multiple antigenic exposures, or to some other mechanisms. The physician and patient should consider that Factor VIII concentrates may be associated with the transmission of AIDS and weigh the benefits of therapy accordingly.

Note:
1. Use separate sheet if space is insufficient for requirements. Continued ...
2. Complete Schedule (attached) with final proposed amendment.

Application is hereby made for the above amendment to be made to the Authorisation.

Date . . 8th April 1987. . . . . Signature GRO-C . . . . . .

Proposed Statement (Cont'd)

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 a haematocrit and direct Coombs test for signs of progressive anaemia.

b. Variation or Additional Information (not requiring Amendment to Schedule) (Relevant documentation should accompany this application)

Subject Matter
(see itemised list)

Item 4(d) - Method of Manufacture

Permission is requested to increase the terminal heat treatment of the final lyophilised product from 60°C for 30 hours to 68°C for 72 hours.

The accompanying documentation confirms that this increase in heat treatment does not adversely affect the structure, stability, safety, half-life or recovery of the Factor VIII. Neoantigens are not formed.

Index of Documents Accompanying this Application

See information accompanying PA 10/6/1.

Signature . . GRO-C . . . . . **Date** . . . 8th April 1987 . . .

c. Office Use Only

Amendment/Variation/Addition No				
Date Received	Date Approved	Initial	Date of Issue to Department of Health	Date of Issue to Company

CHECKLIST **VARIATION (Amendment)**

Item No	Item	Indicate
1.	Name (trading style) and address of Holder	
2.	Product Name	
3.	Drug Substance	
(a)	Source/Manufacturer	
(b)	Method of Manufacture	X
(c)	Impurities	
(d)	Specifications	
(e)	Analytical Methods	
(f)	Other	
4.	Finished Dosage Form	
(a)	Product Form Description	
(b)	Formulation	
(c)	Manufacturer	
(d)	Method of Manufacture	
(e)	Specifications	
(f)	Quality Control Procedures	
5.	Stability	
6.	Containers/Packaging	
7.	Labelling	X
8.	Shelf Life	
9.	Storage Precautions	
10.	Importer/Distributor	
11.	Method of Sale & Supply	

Item No	Item	Indicate
12.	Method of Promotion	
13.	Reconstitution	
14.	Incompatibilities	
15.	Other	
16.	Pharmacodynamic or Kinetic Characteristics	
17.	Clinical Use	
18.	Route of Administration	
19.	Dosage Instructions	
20.	Special Instructions for at risk categories	
21.	Contraindications	
22.	Precautions & Warnings	X
23.	Special Warnings	
24.	Significant side effects	
25.	Use during pregnancy and lactation	
26.	Interactions	

SCHEDULE

Endorsement No: . . . . . .

AMENDMENT TO PRODUCT AUTHORISATION

Product Authorisation No: PA 10/6/2

Product Name: FACTORATE (Double Fill)

Schedule Number & Heading	Amended Statement
B8 Labelling	Labelling The proprietary name and the words "Heat Treated". Precautions & Warnings Isolated cases of Acquired Immune Deficiency Syndrome (AIDS) have been reported in haemophiliacs who have received blood and/or coagulation Factor concentrates including Factor VIII concentrates. It is not known if the disease is due to a transmitted specific agent, the HIV virus, secondary to multiple antigenic exposures, or to some other mechanisms. The physician and patient should consider that Factor VIII concentrates may be associated with the transmission of AIDS and weigh the benefits of therapy accordingly. 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 a haematocrit and direct Coombs test for signs of progressive anaemia.

Form No PA

Application for Variation

Amendment or Addition to Information

Supplied with Product Authorisation Applications

Name of Product FACTORATE **PA Number** PA 10/6/3

Dose Form & Strength 125 ml vials each containing not less than 250, 500 or 1000 International Units of Dried Human Antihaemophilic Fraction.

Name and Address of Product Authorisation Holder

ARMOUR PHARMACEUTICAL COMPANY LIMITED
ST. LEONARD'S HOUSE, ST. LEONARD'S ROAD
EASTBOURNE, EAST SUSSEX, BN21 3YG
ENGLAND.

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1. Amendment/Variation in details of Schedule to Authorisation. (Supportive evidence should accompany this application). (Statements should be given exactly as they appear in the schedule or as it is proposed that they appear).

PA Schedule Item No	Present Statement	Proposed Statement (see note below)
	Present Statement	Proposed Statement
B8	Labelling	Labelling
	The proprietary name.	The proprietary name and the words "Heat Treated".
B15	Precautions & Warnings	Precautions & Warnings
	1. At the present state of technical development it is not yet possible to exclude the possibility of transmission of virus hepatitis. 2. Because of the presence of quantities of A and B iso-haemagglutinins, administration of large volumes of the preparation to patients of blood group A, B or AB may lead to intravascular haemolysis.	Isolated cases of Acquired Immune Deficiency Syndrome (AIDS) have been reported in haemophiliacs who have recieved blood and/or coagulation factor concentrates including Factor VIII concentrates. It is not known if the disease is due to a transmitted specific agent, the HIV virus, secondary to multiple antigenic exposures, or to some other mechanisms. The physician and patient should consider that Factor VIII concentrates may be associated with the transmission of AIDS and weigh the benefits of therapy accordingly.

Note:
1. Use separate sheet if space is insufficient for requirements.
2. Complete Schedule (attached) with final proposed amendment.

Continued ...

Application is hereby made for the above amendment to be made to the Authorisation.

Date 8th April 1987 Signature . GRO-C .....

Proposed Statement (Cont'd)

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 a haematocrit and direct Coombs test for signs of progressive anaemia.

. Variation or Additional Information (not requiring Amendment to Schedule) (Relevant documentation should accompany this application)

Subject Matter
(see itemised list)

Item 4 (d) - Method of Manufacture

Permission is requested to increase the terminal heat treatment of the final lyophilised product from 60°C for 30 hours to 68°C for 72 hours.

The accompanying documentation confirms that this increase in heat treatment does not adversely affect the structure, stability, safety, half-life or recovery of the Factor VIII. Neoantigens are not formed.

Index of Documents Accompanying this Application

See information accompanying PA 10/6/1.

Signature . . . . GRO-C . . . . . **Date** . . 8th April 1987 . . . . . .

c. Office Use Only

Amendment/Variation/Addition No				
Date Received	Date Approved	Initial	Date of Issue to Department of Health	Date of Issue to Company

CHECKLIST **VARIATION (Amendment)**

Item No	Item	Indicate
1.	Name (trading style) and address of Holder	
2.	Product Name	
3.	Drug Substance	
(a)	Source/Manufacturer	
(b)	Method of Manufacture	X
(c)	Impurities	
(d)	Specifications	
(e)	Analytical Methods	
(f)	Other	
4.	Finished Dosage Form	
(a)	Product Form Description	
(b)	Formulation	
(c)	Manufacturer	
(d)	Method of Manufacture	
(e)	Specifications	
(f)	Quality Control Procedures	
5.	Stability	
6.	Containers/Packaging	
7.	Labelling	X
8.	Shelf Life	
9.	Storage Precautions	
10.	Importer/Distributor	
11.	Method of Sale & Supply	

Item No	Item	Indicate
12.	Method of Promotion	
13.	Reconstitution	
14.	Incompatibilities	
15.	Other	
16.	Pharmacodynamic or Kinetic Characteristics	
17.	Clinical Use	
18.	Route of Administration	
19.	Dosage Instructions	
20.	Special Instructions for at risk categories	
21.	Contraindications	
22.	Precautions & Warnings	X
23.	Special Warnings	
24.	Significant side effects	
25.	Use during pregnancy and lactation	
26.	Interactions	

SCHEDULE

Endorsement No: . . . . . .

AMENDMENT TO PRODUCT AUTHORISATION

Product Authorisation No: PA 10/6/3 . . . . . .

Product Name: FACTORATE . . . . . .

Schedule Number & Heading	**Amended Statement**
B8 Labelling	Labelling The proprietary name and the words "Heat Treated". Precautions & Warnings Isolated cases of Acquired Immune Deficiency Syndrome (AIDS) have been reported in haemophiliacs who have received blood and/or coagulation Factor concentrates including Factor VIII concentrates. It is not known if the disease is due to a transmitted specific agent, the HIV virus, secondary to multiple antigenic exposures, or to some other mechanisms. The physician and patient should consider that Factor VIII concentrates may be associated with the transmission of AIDS and weigh the benefits of therapy accordingly. 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 a haematocrit and direct Coombs test for signs of progressive anaemia.