		FORM MLA 201 (revised 1984)
	MEDICINES ACTS 196	
4	APPLICATION FOR A PR	ODUCT LICENCE
I Nema of Droduct	NTIHAEMOPHILIC FACTO OUR-HEAT TREATED HEM	• •
2. Full name and address of proposed licence holder:	TRAVENOL LAE CAXTON WAY, THETFORD, NORFOLK, IP2	BORATORIES LTD., 24 3SE.
3. Trading style to be shown on licence if different from a		/E
<ol> <li>Role of proposed licence hold</li> <li>(please tick in appropriate box(es))</li> </ol>	(1)	as person responsible for composition of product manufactured in UK,
	(11)	in the case of a proprietary medicinal product, as person responsible for placing it on the UK market,
	(111)	as person who imports or procures its importation,
	(1v)	as person who first sells or supplies it as a medicinal product.
<ol> <li>Activities for which licence is required:</li> <li>(please tick in appropriate</li> </ol>	(1)	selling or supplying product in the UK
box(es))	[] (11)	procuring the manufacture or assembly of the product for sale or supply in the UK.
	[] (iii)	importing or procuring the importation of the product.
	(iv)	Other (specify) EXPORTING THE PRODUCT
6. Applicants own reference no	• RA.191A	
	ions: TO VARY PLOII 11 PRODUCTS. THE A	AS MADE IN MAY 1983 AND SEPTEMBER 1984 6/0011 TO INCLUDE A HEAT TREATMENT STEP TTACHED ABRIDGED APPLICATION HAS BEEN CENCE VARIATION.

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8.	To cov before	er sale and supply of the product manuf the grant of the licence:	factur	ed		•	YES/20
9.	Scient	lfic Evidence:	(i)	Chemist	ry and Pharmacy	142	Pages
			(11)		mental and Lcal Studies	222	Pages
			(111)	Clinica	al Trials	88	Pages
10.	infor stand such	a give your consent to the disclosure a mation given in or in connection with a ards applicable to the product or its a information will not be used in the con at prior reference to you?	this a active	pplicati ingredi	lon or to the ph lent on the unde	armace rstand monogr	utical ling that
11.	respe accor	apply for the grant of a product licen ct of the product(s) to which the Product dance with the other particulars annex years and subject to the following pro-	uct Pa ed; th	rticula: e said :	rs in Part lA re	fer an	nd in
	11.1	All the Standard Provisions applicable the time being in force under Section	e to p 47 of	roduct The Me	licences under r licines Act 1968	egulat •	ions for
	11.2	The product shall not be recommended specified in the Product Particulars accordance with the said Product Part time be approved by the licensing aut	as Use icular	s, and s s except	shall be sold or	suppl	lied in
	11.3	The specification of the constituents accordance with the information conta application.	and o ined i	f the find t	inished product rnished in conne	shall	be in with the
 2) 	11.4	The product is to be manufactured onl this application or furnished in conn	y in a ection	ccordan with i	ce with the meth t.	ods se	et out in
	11.5	No material information has been omit	ted (w	ithin t	he knowledge of	the si	Ignatory).
	Dato	Jack, November 1987	Sta	nature	GRO-C		
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St	ate ca	pacity in which signed					
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Page 2	
(Official use only)	
Form MLA 201	
PRODUCT PARTICULARS - a complete set of pages should be included for each strength of produc	:t
PL Number of Product: (Official use only)	
ANTIHAEMOPHILIC FACTOR (HUMAN) 1. Name of Product and Strength: METHOD FOUR-HEAT TREATED HEMOFIL-T	
(Official use only)	
2. Description of Pharmaceutical form (eg tablet, slow-release tablet, capsule etc): A STERILE LYOPHILISED POWDER WHICH IS RECONSTITUTED WITH WATER FOR INJECTIONS PH.EUR. PRIOR TO INTRAVENOUS ADMINISTRATION.	ميدينية بدهيية لمتياهد فيستجد فيستبد فالمتيابة ومتواجد
(Official use only)	
3a. Legal status (place tick in appropriate box(es)) (Official use only)	
Prescription Pharmacy General Sales	
3b. Method of retail sale or supply: BY PRESCRIPTION THROUGH HOSPITALS, PHARMACIES AND CLINICS	
(Official use only) Text should be completed in block capitals	

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•	D			]	(Official use only)			I		I			-			
	4	•	Ac	tiv	e Constituents:											
				ial ly)	Name	id	eci ati	on		Ou	Un	ity it uan	or		Un	it
					HUMAN COAGULATION FACTOR VIII (MIN)		E	P	2	2	5				1	U
		1	1		DERIVED FROM SOURCE PLASMA HUMAN OR (MIN)		1	I		T	0				1	U
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- 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.

	(Officia	l use on	1y)	
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#### Recommended clinical indications, and route(s) of administration:

THE USE OF ANTIHAEMOPHILIC FACTOR (HUMAN), HEMOFIL T, IS INDICATED IN HAEMOPHILIA A (CLASSICAL HAEMOPHILIA) FOR THE PREVENTION AND CONTROL OF HAEMORHAGIC EPISODES.

THE CONCENTRATE CAN BE OF SIGNIFICANT THERAPEUTIC VALUE IN PATIENTS WITH ACQUIRED FACTOR VIII INHIBITORS NOT EXCEEDING 10 BETHESDA UNITS PER ML. HOWEVER, IN SUCH USES THE DOSAGE SHOULD BE CONTROLLED BY FREQUENT LABORATORY DETERMINATIONS OF CIRCULATING FACTOR VIII.

ANTIHAEMOPHILIC FACTOR (HUMAN) IS NOT INDICATED IN VON WILLEBRAND'S DISEASE.

ANTIHAEMOPHILIC FACTOR (HUMAN), HEMOFIL T IS TO BE ADMINISTERED ONLY BY THE INTRAVENOUS ROUTE.

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All entries must be made in full. Cross references, eg. to an accompanying data sheet 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.

Page 4

(Official use only)	age 5
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6. Recommended doses and dosage schedules:	
Distinguish between adults, children and the elderly and between different clinical indications EACH BOTTLE OF ANTIHAEMOPHILIC FACTOR (HUMAN), METHOD FOUR, HEAT-TREATED, HEMOFIL T, IS LABELLED WITH THE NUMBER OF AHF WHICH IT CONTAINS, 1 AHF UNIT BEING DEFINED AS THE ACTIVITY (Official IN 1 ML OF NORMAL POOLED HUMAN PLASMA LESS THAN 1 HOUR OLD use only) LEVEL).	UNITS PRESENT
ABILDGAARD, ET AL REPORTED THAT INFUSION OF 1 UNIT OF AHF PER KG BODY WI CONSISTENTLY PRODUCES AN INCREASE OF 2% (OF NORMAL), WHILE SHANBROM AND FOUND THAT 3.8 TO 4.0 UNITS PER KG. PRODUCE AN INCREASE OF 10% (OF NORM AHF LEVEL. (THE FORMER AUTHORS WORKED WITH BOYS 8 MONTHS TO 14 YEARS OF WHILE THE LATTER WORKED PRIMARILY WITH ADULTS). THE FOLLOWING FORMULAE THEREFORE BE USED TO CALCULATE, APPROXIMATELY, THE EXPECTED RESPONSE FRO GIVEN DOSE OR THE DOSE REQUIRED FOR A GIVEN EFFECT;	THELIN AL) IN F AGE, CAN
I. UNITS REQUIRED = BODY WEIGHT (IN KG) $\times$ 0.4 $\times$ DESIRED AHF INCREASE ( II. EXPECTED AHF INCREASE (IN % OF NORMAL) = UNITS ADMINISTERED	NORMAL)
THE DATA OF ABILDGAARD, ET AL WOULD CALL FOR A FACTOR OF 0.5 INSTEAD OF THE PRECEDING FORMULAE.	
(Official use only)	
7. Name(s) of manufacturer(s) of the dosage form and site(s) of manufacture: HEMOFIL T	
HYLAND DIVISION,AND/ORN.V. TRAVENOL LABORATORITRAVENOL LABORATORIES INC.,BOULEVARD D'HOURAING,4501 COLORADO,7860 - LESSINES,LOS ANGELES,BELGIUM.CALIFORNIA 90039.WATER FOR INJECTIONS PH. EUR.	ES S.A.,
PHARMA HAMELN, 3250 HAMELN 1, (ADERDE), WEST GERMANY. AND/OR AND/OR AND/OR AND/OR N.V. TRAVENOL LABORATORI BOULEVARD D'HOURAING, 7860 - LESSINES, BELGIUM.	ES S.A.,

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KA A FC OF SF BI WI MA	ASPER HA SINGLE AEMORRHA DR OPTIN F FACTO ROCEDUR HOULD B LOOD WE HEN THE AINTAIN AYS.	AS FO INFU AGES, MUM C R VII E. A E GIV RE LC PATI ED AT	ISION A LOT I, SE /EN ENT F A	N IF FACT FOR TO COND ABOU DURI REA DAIL	A L OR V MATI ACHI DOS T 5 NG T CHES Y MI	EVEI ON. EVE E OI HOU THE NIM	LOF LEV AL FFA RSA OPER ERE UMO	30% EL 0 SUR EVEL CTOP FTEP ATIC COVE F AT	GOR OF 35 RGERY OF VII THE ON, A ERY F LEA	MORE TO KA 80 T I HA PRI THI COM. AST 3	IS / 50% / SPER 0 10 LF T MING RD D TH 0% F	ATTA OF N REC 0%, HE S DOS OSE E FA OR A	INE IORM BE IZE OF ACTO A HE	D. IAL GIV OF IF CON OR V	FO SHO S T EN TH SE CEN III NG	R MI ULD HAT AN E P VER TRA LE PER	DRE BE TH HOU RIM AL TE VEL IOD	SER OBT E FI R BE ING UNIT SHOU SHOU OF	AIN RST FOR DOS S 0 ILD 10	S ED DOS E TH E F BE ( BE TO	E IE IVE 4	N
E	XACT DO	SAGE	DET	ERMI	NATI	ONS	SHO	ULD	BE N	<b>1ADE</b>	BASE	D OI	N TH	IE N	EDI	CAL	JU	DGME	NT	OF 1	THE	
PI	HYSICIA ND THE	N REC DESII	GARD RED	ING	CIRC	UMS F FA	TANC	ES, VII	CONI II TO	DITIO	N OF	ΡA	LIEN	IT,	DEG	REE	OF	DEI	· 1 C I	ENC	(,	
A	HYSICIA ND THE ial use	DESII	RED	ING	CIRC	F FA	TANC	ES, VII		DITIO	N OF	ΡA	LIEN	IT,	DEG	REE		DEI	- 1 C I	ENC	<b>,</b>	
A	ND THE	DESII	RED	ING	CIRC	UMS FA	TANC	ES, VII		DITIO	N OF	ΡA	LIEN	ιΤ, 	DEG	REE		DEF		ENC	<b>(</b> , )	
A	ND THE	DESII	RED	ING	CIRC	UMS FA	TANC	ES, VII		DITIO	N OF	ΡA	LIEN		DEG	REE		DEF		ENC	<b>(</b> ,	
A	ND THE	DESII	RED	ING	CIRC		TANC	ES, VII		DITIO	N OF	ΡA	LIEN		DEG	REE		DEF		ENC	<b>(</b> ,	
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	nded doses schedules:	and			<u></u>	
Disting and bet	iish betwee ween differ	en adults, cl rent clinica:	hildren and t l indications	the elderly s		
(Offici	INTRA APPRO	VENOUS ROUTE	E. THE MATE		ADMINISTERED C BE RECONSTITUT NS PH.EUR.	
	PREPA	MORE AHF UN	ITS PER ML M	UST BE ADMINI	HUMAN), HEMOFI ISTERED AT CAF F 2 ML PER MIN	EFULLY
						IVEN RAPIDLY,
AND DUP	ING ADMINI	STRATION OF	THE AHF CON	CENTRATE. SH		SE RATE BEFORE ICANT INCREASE NUE.
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Official us	<pre>&gt; only)  </pre>					
	······					
• Name(s)	of manufac	turer(s) of	the dosage i	Form and site	(s) of manufac	ture:
				•		

### 8. Contraindications, Precautions and Warnings: CONTRAINDICATIONS

(Official use only)

NONE KNOWN.

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#### PRECAUTIONS

(Official use only)

THIS ANTIHAEMOPHILIC FACTOR (HUMAN) PREPARATION CONTAINS BLOOD GROUP ISOAGGLUTININS (ANTI-A AND ANTI-B). WHEN LARGE OR FREQUENTLY REPEATED DOSES ARE NEEDED, AS WHEN INHIBITORS ARE PRESENT OR WHEN PRE AND POST-SURGICAL CARE IS INVOLVED, PATIENTS OF BLOOD GROUPS A, B, AND AB SHOULD BE MONITORED FOR SIGNS OF INTRAVASCULAR HAEMOLYSIS AND DECREASING HAEMATOCRIT VALUES. HAEMOLYTIC ANAEMIA, WHEN PRESENT, MAY BE CORRECTED BY THE ADMINISTRATION OF COMPATIBLE GROUP O RED BLOOD CELLS (HUMAN).

IDENTIFICATION OF THE CLOTTING DEFICIENCY AS ONE OF FACTOR VIII IS ESSENTIAL BEFORE THE ADMINISTRATION OF ANTIHAEMOPHILIC FACTOR (HUMAN) IS INITIATED.

SINCE ANTIHAEMOPHILIC FACTOR (HUMAN), METHOD FOUR, HEAT-TREATED, HEMOFIL T, CONTAINS SMALL RESIDUAL AMOUNTS OF FIBRINOGEN WHICH TEND TO CAUSE THE GROUND SURFACE OF GLASS TO STICK, PLASTIC (DISPOSABLE) SYRINGES SHOULD BE USED.

ALLERGIC REACTIONS MAY BE ENCOUNTERED FROM THE USE OF AHF CONCENTRATE PREPARATIONS.

ALTHOUGH DOSAGE CAN BE ESTIMATED BY CALCULATION, IT IS STRONGLY RECOMMENDED THAT WHENEVER POSSIBLE, APPROPRIATE LABORATORY TESTS BE PERFORMED ON THE PATIENT'S PLASMA AT SUITABLE INTERVALS TO ENSURE THAT ADEQUATE AHF LEVELS HAVE BEEN REACHED AND ARE MAINTAINED.

IF THE AHF LEVEL FAILS TO REACH EXPECTED LEVELS OR IF BLEEDING IS NOT CONTROLLED AFTER APPARENTLY ADEQUATE DOSAGE, THE PRESENCE OF INHIBITOR SHOULD BE SUSPECTED. BY APPROPRIATE LABORATORY PROCEDURES, THE PRESENCE OF INHIBITOR CAN BE DEMONSTRATED AND QUANTIFIED IN TERMS OF AHF UNITS NEUTRALISED BY EACH ML OF PLASMA OR BY THE TOTAL ESTIMATED PLASMA VOLUME. AFTER SUFFICIENT DOSAGE TO NEUTRALISE INHIBITOR, ADDITIONAL DOSAGE PRODUCES PREDICTED CLINICAL RESPONSE. IT SHOULD BE NOTED THAT WHEN INHIBITOR IS PRESENT, MEASUREMENT OF LEE-WHITE CLOTTING TIME MAY BE A BETTER INDEX OF ADEQUACY OR DOSAGE THAN MEASUREMENT OF CIRCULATING AHF.

Page 6

	(Official us	e only)		Page b
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8. Contraindications, Precautions and Warnings:

#### WARNINGS

(Official use only)

THIS CONCENTRATE IS PREPARED FROM LARGE POOLS OF FRESH HUMAN PLASMA WHICH MAY CONTAIN CAUSATIVE AGENTS OF VIRAL HEPATITIS. HOWEVER, EACH UNIT OF PLASMA USED IN THE MANUFACTURE OF THIS PRODUCT HAS BEEN FOUND TO BE NONREACTIVE FOR HEPATITIS B SURFACE ANTIGEN (HBSAG) WHEN TESTED WITH LICENCED THIRD GENERATION REAGENTS. IN ADDITION, THIS PRODUCT HAS BEEN SUBJECTED TO A HEATING PROCEDURE DURING ITS MANUFACTURING PROCESS DESIGNED TO REDUCE THE RISK OF TRANSMISSION OF HEPATITIS. ALTHOUGH THESE TESTING AND HEATING STEPS REDUCE THE RISK OF HEPATITIS TRANSMISSION, THE POSSIBILITY OF SUCH TRANSMISSION SHOULD BE CONSIDERED IN USE OF THE PRODUCT.

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9.	Other	constituents:											
	fficial e only)	Name	1	ic	eci: ati ere	on	m	bđ	anti Uni % qu	to	r	Un	it
		HEPARIN, SODIUM		U	s	P	Q	s					
$\Box$		SODIUM CITRATE		U	S	P	Q	s					
		(	DR		E	Р							
		GLYCINE		U	S	_ <b>P</b> ,	Q	s		•			
		. (	OR		В	Р			<u> </u>				
Ń		POLYETHYLENE GLYCOL		N	F		Q	s		•			
			OR	D	Α	В				¢			
		SODIUM CHLORIDE		U	s	Р	Q	s					
			OR		E	Р				•			
		SODIUM HYDROXIDE			N	F	Q	s		<u> </u>			
			OR		В	Р				•			
		ACETIC ACID		U	s	Р	0	s		•			
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		WATER FOR INJECTION	OR	U	S	Р	Q	s		ł			
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(Official use only)

- 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.

<u>H 1 </u>	(Official use only)
10. Descri	ption of essential processes in the manufacture:
CRYOP INACT AFTER	E PLASMA (HUMAN) IS THAWED CAREFULLY AND CENTRIFUGED TO REMOVE THE RECIPITATE WHICH IS THEN DISSOLVED IN HEPARINISED GLYCINE CITRATED SALINE. IVE PROTEINS ARE PRECIPITATED OUT WITH P.E.G. AND REMOVED BY CENTRIFUGATION. FURTHER PURIFICATION THE FACTOR VIII RICH PORTION IS DISSOLVED IN CITRATED E SOLUTION AND CLARIFIED BY CENTRIFUGATION AND/OR FILTRATION.
THEN STOPP	RODUCT IS THEN STERILISED BY FILTRATION THROUGH A 0.22 UM FILTER MIXED AND DISPENSED ASEPTICALLY INTO STERILE GLASS VIALS. STERILE LYOPHILISATION ERS ARE PARTIALLY INSERTED AND THE PRODUCT FROZEN AND THEN FREEZE DRIED. AFTER ILISATION THE STOPPERS ARE SEATED UNDER VACUUM AND CAPPED.
	IALS ARE FURTHER PROCESSED BY HEATING AT 60°C $\pm$ 1°C FOR 72 HOURS IN A WATER AND THEN INSPECTED, LABELLED AND PACKAGED.
STOPP	VIALS ARE STERILISED BY DRY HEAT AT 200°C FOR A MINIMUM OF 175 MINS, ERS ARE STERILISED BY STEAM AT 121°C FOR A MINIMUM OF 44 MINS,PRIOR LING.
·····	
	ed Product Specification:
2. 3. 4.	oH - 6.8 to 7.4 MOISTURE - MAX. 2% SOLIBILITY - COMPLETE DISSOLUTION WITHIN 600 SECS. AT 20 - 25°C TOTAL PROTEIN - MAX 1.75 MG PROTEIN PER I.U. GLYCINE - MAX. 0.50 M
6.	
-	POLYETHYLENE GLYCOL - MAX 1.5 G/L STERILITY - STERILE
	STERILITY - STERILE PYROGENS - NON PYROGENIC TOXICITY - MICE - NO SIGNIFICANT SYMPTOMS
9. 10. 11.	STERILITY - STERILE PYROGENS - NON PYROGENIC TOXICITY - MICE - NO SIGNIFICANT SYMPTOMS GUINEA PIGS - NO SIGNIFICANT SYMPTOMS NATURAL ANTI-A OR ANTI-B TITRE - 1:160 MAX. IMMUNE ANTI-A OR ANTI-B TITRE - 1:640 MAX.
9. 10. 11. 12. 13.	STERILITY - STERILE PYROGENS - NON PYROGENIC TOXICITY - MICE - NO SIGNIFICANT SYMPTOMS GUINEA PIGS - NO SIGNIFICANT SYMPTOMS NATURAL ANTI-A OR ANTI-B TITRE - 1:160 MAX. IMMUNE ANTI-A OR ANTI-B TITRE - 1:640 MAX. HEPATITIS B SURFACE ANTIGEN - NON REACTIVE HEPARIN - 1.0 UNIT/ML PROTEIN IDENTITY - HUMAN: POSITIVE
9. 10. 11. 12. 13. 14.	STERILITY - STERILE PYROGENS - NON PYROGENIC TOXICITY - MICE - NO SIGNIFICANT SYMPTOMS GUINEA PIGS - NO SIGNIFICANT SYMPTOMS NATURAL ANTI-A OR ANTI-B TITRE - 1:160 MAX. IMMUNE ANTI-A OR ANTI-B TITRE - 1:640 MAX. HEPATITIS B SURFACE ANTIGEN - NON REACTIVE HEPARIN - 1.0 UNIT/ML
9. 10. 11. 12. 13. 14.	STERILITY - STERILE PYROGENS - NON PYROGENIC TOXICITY - MICE - NO SIGNIFICANT SYMPTOMS GUINEA PIGS - NO SIGNIFICANT SYMPTOMS NATURAL ANTI-A OR ANTI-B TITRE - 1:160 MAX. IMMUNE ANTI-A OR ANTI-B TITRE - 1:640 MAX. HEPATITIS B SURFACE ANTIGEN - NON REACTIVE HEPARIN - 1.0 UNIT/ML PROTEIN IDENTITY - HUMAN: POSITIVE BOVINE: NEGATIVE POTENCY - 10 ML SIZE: MIN 225 1.U./VIAL

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	(Official use only)	Page 9
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2.	TRAVENOL LABORATORIES INC., 4501 COLORADO, LOS ANGELES, AND/OR TRAVENOL LABORATORIES S.A.,	13. Arrangements for storage: THE FINISHED PRODUCT MAY BE STORED AT THE MANUFACTURING FACILITIES DETAILED ABOVE OR IN LICENCED WHOLESALE PREMISES
4.	7860 LESSINES, BELGIUM. Importer: TRAVENOL LABORATORIES LTD., CAXTON WAY, THETFORD, NORFOLK.	IN THE U.K. (WHOLESALE DEALERS LICENCE WL01 0 15. List other countries of registration: WEST GERMANY, U.S.A., CANADA, SPAIN, BELGIUM, SWEDEN, IRELAND - LICENCE TO IMPORT GRANTED IN HOLLAND
6.	Site and Arrangements for Ouality Cont QUALITY CONTROL WILL BE CARRIED OUT /	rol: AT THE PLACE OF MANUFACTURE. THE LICENCE ING IF A BATCH IS OF ACCEPTABLE QUALITY
17.	Type of container(s), pack size(s), sh 10 ML AND 30 ML GLASS VIALS OF ANTIHAEMOPHILIC FACTOR (HUMAN) METHOD FOUR, DRIED, HEAT TREATED, HEMOFIL T.	elf life and storage precautions: (Official <u>Container Size</u> <u>Unit</u> <u>use only</u> )       0 M L
2	10 ML AND 30 ML GLASS VIALS OF WATER FOR INJECTIONS PH.EUR. SHELF LIFE IS 24 MONTHS. PRODUCT SHOULD BE STORED AT 2-8°C AND MAY BE STORED AT ROOM TEMPERATUR FOR UP TO ONE MONTH WITHIN THE DATIN PERIOD.	
No	FREEZING SHOULD BE AVOIDED TO PREVEN BREAKAGE OF THE DILUENT BOTTLE. Dte: Please tabulate data in space all Where applicable enter unit as MO	Lowed.

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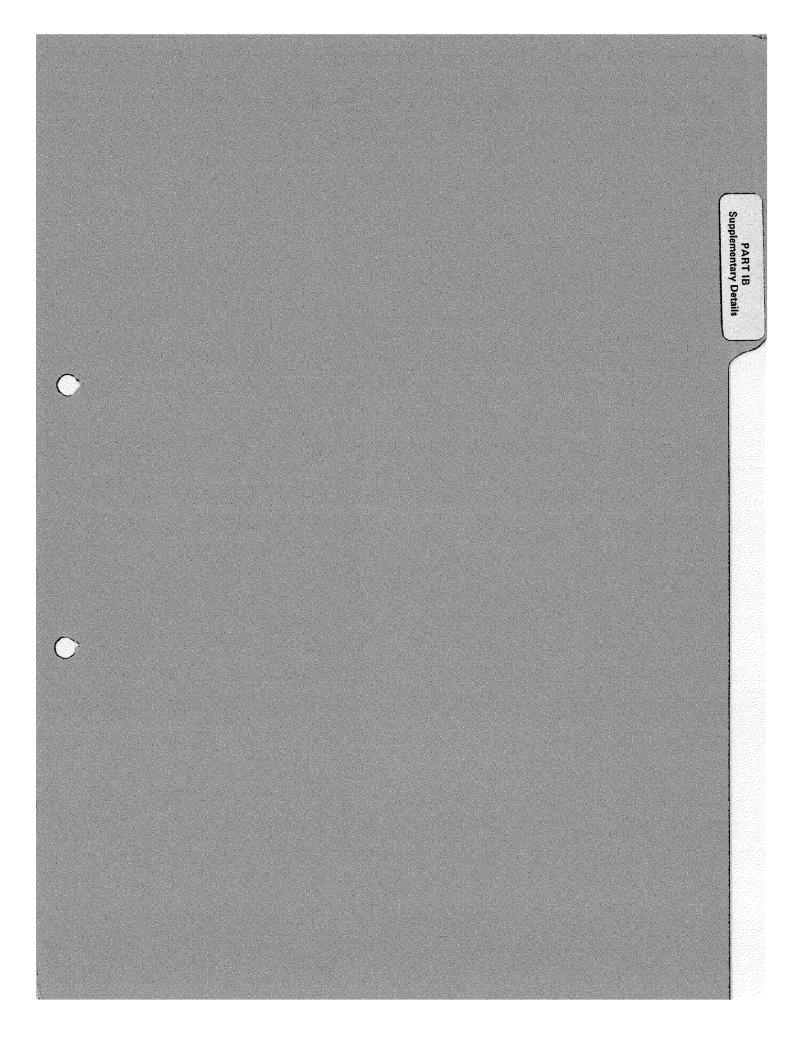
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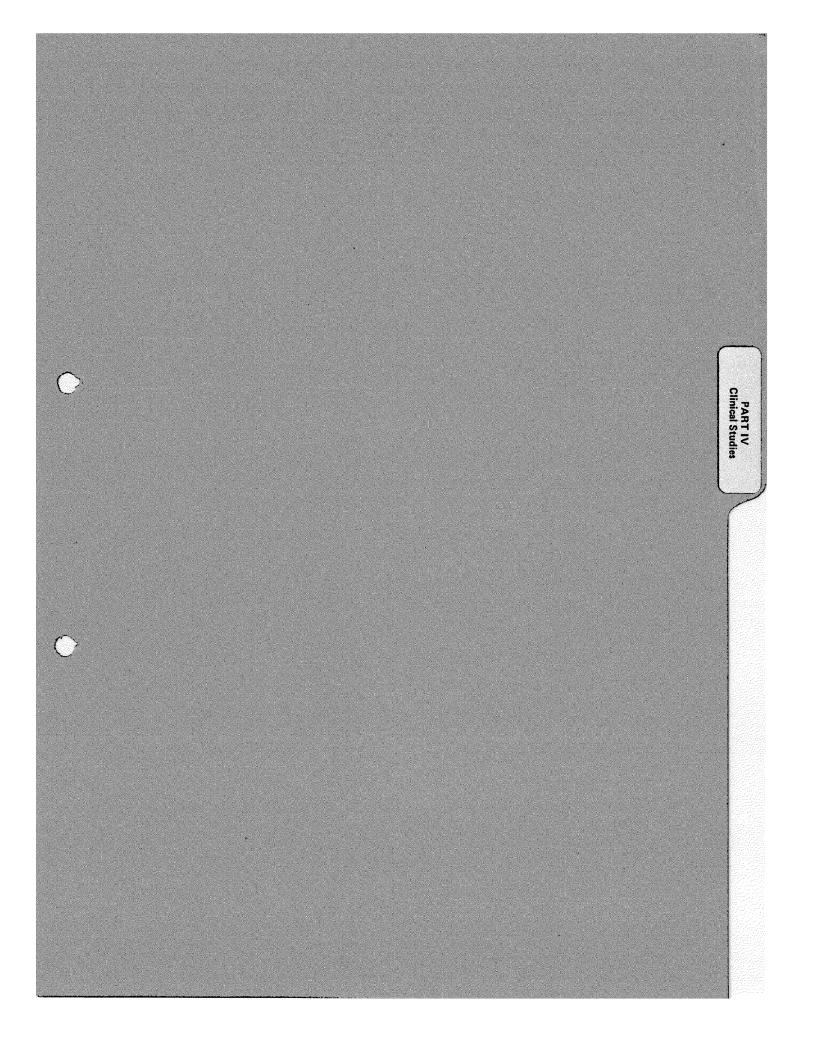
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### TABLE OF CONTENTS

Section

Page Number

### PART 1B - SUPPLEMENTARY DETAILS

- 1. <u>Product Literature</u>
  - 1.1 Labelling and Package Inserts
  - 1.2 Data Sheets
- 2. Background
  - 2.1 Applications in Other Countries
  - 2.2 Background
- 3. Persons Involved in the Manufacture of the Finished Product and its Distribution in the U.K.
  - 3.1 Manufacturer and Assembler
  - 3.2 Arrangements for Storage
  - 3.3 Importer

( )

3.4 Responsibility for Quality Control

APPENDIX	I	:	PROPOSED	TEXT	FOR	CONTAINER	3
APPENDIX	II	:	PROPOSED	TEXT	FOR	CARTON	6
APPENDIX	III	:	PROPOSED	TEXT	FOR	DIRECTION SHEET	11
APPENDIX	IV	:	PROPOSED	TEXT	FOR	DATA SHEET	21

#### PART 1B - SUPPLEMENTARY DETAILS

- 1. Product Literature
  - 1.1 Labelling and Package Inserts

The proposed text for the container label is included in Appendix I

The proposed text for the carton is included in Appendix II

The proposed direction sheet is included in Appendix III

1.2 Data Sheets

The proposed text for the data sheet for this product is included in Appendix IV

#### 2. Background

### 2.1 Application in Other Countries

Hemofil-T is currently licenced for sale in West Germany, U.S.A., Canada, Spain, Sweden, Belgium and Ireland. A licence to import has been granted in Holland.

### 2.2 Background

HEMOFIL Antihaemophilic Factor (Human) Method Four is currently licenced for sale under PL0116/0011. This licence was first granted on 19th February, 1973 and renewed on 19th February, 1978. Application for the second renewal was submitted on 16th December, 1982, however, the Department requested that the application be resubmitted under the Review/Renewal on Expiry of Existing Licence (MLA.201R) and this was sent on 26th October, 1983.

A variation to our existing licence to include a heat treatment step was submitted on 11th May, 1983. We received notification from the Department (letter dated 14th October, 1983) that the Committee on Safety of Medicines had refused the variation application on the following grounds:

- 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.

On further discussion with the Medicines Division it was requested that we submit an abridged licence application to cover the treated product Antihaemophilic Factor (Human) Method Four-Heat Treated HEMOFIL-T.

3. <u>Persons Involved in the Manufacture of the Finished product</u> and its Distribution in the U.K.

#### 3.1 Manufacturer and Assembler

Manufacture, assembly, heat treatment and packaging of Antihaemophilic Factor (Human) Method Four, dried, heat treated HEMOFIL T into the final containers is accomplished in the facilities of:

TRAVENOL LABORATORIES S.A. B-7860 Lessines, Belgium a wholly owned subsidiary of Travenol Laboratories, Inc., U.S.A. The product is processed and tested in accordance with requirements established in the Belgian Manufacturing Licence nr 395 ED 402 F 12.

HYLAND THERAPEUTICS DIVISION TRAVENOL LABORATORIES INC., Glendale, California, U.S.A. The product is processed and tested in accordance with the requirements established by the United States Food and Drug Administration and manufactured under U.S. Licence nr 140.

3.2 Arrangements for storage

The finished products may be stored at the manufacturing facilities detailed above or in licenced wholesale premises in the United Kingdom.

Wholesale dealers licence number WL/0116/001.

3.3 Importer

As licence holder.

- 3.4 Responsibility for Quality Control
  - Each manufacturer will be responsible for deciding if a batch of product is of acceptable quality for release.

The licence holder will be responsible for release of product within the United Kingdom.

b) Quality Control will be carried out at the place of manufacture.

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# APPENDIX I

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### : PROPOSED TEXT FOR LABEL

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# APPENDIX II : PROPOSED TEXT FOR CARTON

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PRINTED PACKAGE MATERIAL SPECI	FICATION
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1	ANT	THAEMOP		ACTOR(HUMAN)	), HEAT	T TRE	TED STYLE			
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DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III. PRODUCTION CONTROL, PURCHASING

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EDITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV
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¥		:	30 ml si	ze, dr:	ied		List	No. KD060-639	)		
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9

PRINTED	PACKAGE	MATERIAL	SPECIF	ICATION

DITION	PAGE V	OF V	SUPERSEDES	LIST NO.	PART NO.	REV.
ITEM						
PRODUCT						

30 ml size, dried

List No. KD060-639

#### ANTIHAEMOPHILIC FACTOR (HUMAN)

#### HEMOFIL T

Method Four

COPY AND ARTWORK

Heat Treated

This lot contains: International Units of AHF activity per vial

Expiry Date:

Contents: One bottle 30 ml dried Antihaemophilic Factor (Human), one bottle 30 ml Water for Injections Ph.Eur., one double-ended needle, one filter spike, directions for use.

For intravenous administration.

Administration: See enclosed direction sheet and use as directed by physician. Stabilised with heparin, not over 1.0 unit (0.010 mg) per m) of reconstituted material. Contains no preservative. Use promptly (within 3 hours) after reconstitution. Do not use if gel forms on reconstitution.

WARNING: Plasma from which this product was derived was found to be nonreactive for hepatitis B surface antigen (HBsAG) when tested with licenced third generation reagents. In addition, the process used in the manufacture of this product includes a heating step designed to minimise the risk of transmission of hepatitis. However, no procedure has been shown to be totally effective in removing hepatitis infectivity from Antihaemophilic Factor (Human).

Distributed by: TRAVENOL LABORATORIES LTD., Thetford, Norfolk, England.

PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

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10

APPENDIX III

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### : PROPOSED TEXT FOR DIRECTION SHEET

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		PAGE	°F9	SUPERSEDES	LIST	NO. BASIC	PART NO.		RE
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				HEMOFIL T	JMAN) Metr	od Four, Drie	<u>a</u>		
	•	<ul> <li>package</li> </ul>	label: e of /	s. See instr	uctions g	duct is given iven under DO tency-related	SAGE AND ADI	MINISTRATION	
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		DESCRIPT	ION						
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ED	ITION	PAGE	OF	SUPERSEDES	LIST NO.	PART NO.	REV.
	ITEM						
	PRODUCT						
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A change has been made in the manufacture of this product to include a heating step designed to reduce the risk of transmission of hepatitis. No procedure has been shown to be totally effective in removing hepatitis infectivity from Antihaemophilic Factor (Human). (See Section on CLINICAL PHARMACOLOGY).

#### CLINICAL PHARMACOLOGY

Antihaemophilic factor (AHF) is a protein found in normal plasma which is necessary for clot formation. The administration of Antihaemophilic Factor (Human), HEMOFIL T, provides an increase in plasma levels of AHF and can temporarily correct the coagulation defect of patients with haemophilia A (classical haemophilia).

The half-life of AHF administered to haemophiliacs has been variously estimated at 8 to 24 hours.<sup>2-6</sup> In the severe haemophiliac, the half-life of the first dose of AHF in any form appears to be at the lower end of the range, but for subsequent doses it may be safely estimated as at least 12 to 15 hours in the absence of inhibitors and "active bleeding".

An assessment of the efficacy of the heating step employed was performed by administration to chimpanzees of Antihaemophilic Factor (Human) inoculated with 300 and 30,000 infectious units of hepatitis B. While there was no effect of heating on the high dose inoculum, the chimpanzees receiving 300 infectious units did not develop hepatitis B markers until  $7\frac{1}{2}$  and 10 months had elapsed, as compared to 4 months for untreated material, which may indicate a reduction in infectivity of the product for hepatitis B. The study also indicated that the heat treatment eliminated an unknown quantity of at least one type of non-A, non-B hepatitis virus present in the administered Antihaemophilic Factor (Human).

In addition to the chimpanzee study described above, the effectiveness of the heating step was also assessed by in vitro viral inactivation studies, using, as a marker, a virus which is not commonly found in plasma. When known quantities of Sindbis virus were added to the product, it was shown that the heat treatment employed was capable of inactivating approximately 3.2 logs of this virus.

#### INDICATION AND USAGE

CCPY AND ARTWORK

The use of Antihaemophilic Factor (Human), HEMOFIL T, is indicated in haemophilia A (classical haemophilia) for the prevention and control of haemorrhagic episodes.

PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE
PACKAGE DEVELOPMENT	DATE	QUALITY ASSURANCE	DATE

DISTRIBUTION: INSPECTIONS, PACKAGE DEVELOPMENT, PRODUCTION III' PRODUCTION CONTROL, PURCHASING

13

ITION	PAGE	OF 9	SUPERSEDES	LIST NO.	PART NO.	REV.
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PRODUCT						
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	acquired However,	Facto in su	r VIII inhibi ch uses the d	tors not exceedi	peutic value in patients ng 10 Bethesda Units per controlled by frequent ctor VIII.	
	Antihaem disease.	-	c Factor (Hum	an) is not indic	ated in von Willebrand's	
	CONTRAIN	DICATI	ONS			
	None kno	wn.				
D'	WARNINGS					
	which ma unit of be nonre licenced subjecte designed these te transmis	y cont plasma active third d to a to re sting sion,	ain causative used in the for hepatiti generation r heating proc duce the risk and heating s	agents of viral manufacture of t s B surface anti eagents. In add edure during its of transmission teps reduce the	els of fresh human plasma hepatitis. However, eac his product has been four gen (HBsAg) when tested w lition, this product has h manufacturing process of hepatitis. Although risk of hepatitis mission should be conside	nd to vith been
	PRECAUTI	ONS				
	General					
	isoagglu doses ar post-sur should b decreasi	tinins e need gical e moni ng hae d by t	(anti-A and led, as when i care is invol tored for sig matocrit valu	anti-B). When 1 nhibitors are pr ved, patients of ns of intra-vasc es. Haemolytic	ation contains blood group arge or frequently repeat cesent or when pre- and blood groups A, B and Al cular haemolysis and anaemia, when present, ma ole Group O Red Blood Cell	ted B ay be
		l befo			as one of Factor VIII is Lhaemophilic Factor (Human	n) is
	contains	s small surface	residual amo	unts of fibrinog	od Four, Heat-Treated, HE gen which tend to cause th (disposable) syringes show	he
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#### Laboratory Tests

Although dosage can be estimated by the following calculations, it is strongly recommended that whenever possible, appropriate laboratory tests be performed on the patient's plasma at suitable intervals to ensure that adequate AHF levels have been reached and are maintained.

If the AHF level fails to reach expected levels or if bleeding is not controlled after apparently adequate dosage, the presence of inhibitor should be suspected. By appropriate laboratory procedures, the presence of inhibitor can be demonstrated and quantified in terms of AHF units neutralised by each ml of plasma or by the total estimated plasma volume. After sufficient dosage to neutralise inhibitor, additional dosage produces predicted clinical response. It should be noted that when inhibitor is present, measurement of Lee-White clotting time may be a better index of adequacy of dosage than measurement of circulating AHF.

#### Pregnancy

Animal reproduction studies have not been conducted with Antihaemophilic Factor (Human). It is also not know whether Antihaemophilic Factor (Human) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Antihaemophilic Factor (Human) should be given to a pregnant woman only if clearly needed.

#### ADVERSE REACTIONS

Allergic reactions may be encountered from the use of AHF concentrate preparations.

#### DOSAGE AND ADMINISTRATION

Each bottle of Antihaemophilic Factor (Human), Method Four, Dried, Heat-Treated, HEMOFIL T, is labelled with the number of AHF units which it contains, 1 AHF unit being defined as the activity present in 1 ml of normal pooled human plasma less than 1 hour old (100% AHF level). The stated potency is expressed in International Units of AHF activity and is based upon the use of a standard traceable to the World Health Organisation International Standard for blood coagulation Factor VIII (Human).

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PRODUCT						
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	weight co Shanbrom	nsiste and Th	ntly produces elin found	an increase of that 3.8 to 4.0	of l unit of AHF per E 2% (of normal), whi D units per kg produc	lle ce an
					(The former authors le the latter worked	
	calculate	e, appr		e expected resp	therefore be used to ponse from a given do	ose or the
	I. Unit	s requ	ired=			
1			weight (in kg ed AHF increa	;) x 0.4 x ise (in % of no:	rmal)	
	Exan	mple:	70 x 0.4 x 50	) = 1,400 units		
	II. Expe	ected A	HF increase (	in Z of normal	) =	
		<u>units</u> body	administered weight (in kg	<u>1</u> 5) x 0.4	· · · · · · · · · · · · · · · · · · ·	
	Exan	mple:	$\frac{1,400}{70 \times 0.4} = 5$	50%	•	
			ldgaard, et a eding formula		or a factor of 0.5 in	nstead of
	varies wi	ith cir	cumstances ar	nd with the pat	ires for normal haemo ient. The amount of eficiency and on the	factor to
	with a si serious h be obtain that the given an	ingle in naemorn ned fon first hour h	infusion if a chages, a Fact c optimum clot dose of Facto pefore the pro	level of 30% of for VIII level formation. In for VIII, to ach occdure. A sec	pisodes will general r more is attained. of 35 to 50% of norma n surgery, Kasper re- ieve a level of 80 to ond dose of Factor V	For more al should commends o 100%, be III half
	priming of a third of recovery	dose. dose of room.	If several un concentrate The Factor V	nits of blood w should be give VIII level shou	en about 5 hours after re lost during the op n when the patient re ld be maintained at od of 10 to 14 days.	peration, eaches the
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			<u>e de presidente de co</u>				
	gui Hil ble	deline gartne eding	e. 10th er, 12	her dosage reg which outlines des, and Schim	imens have bee dosage accord	d as a reference and a n proposed such as that ing to the various types hich describes continuou	s of
	of	the ph	ysici	an regarding o	ircumstances,	based on the medical ju condition of patient, do actor VIII to be achieved	egree
	Rec	onstit	ution	: Use Aseptic	: Technique		
	1.					HEMOFIL T, (dry concent luent) to room temperate	
	2.			ps from concer f rubber stopp		ent bottles to expose co	entral
	3.	Clea	anse s	toppers with g	germicidal solu	tion.	
	4.	usi	ng car		n the exposed e	nd of double-ended need and. Insert exposed need	
	5.	usi upr: need	ng ase ight c ile th	ptic technique oncentrate bot rough the cond	es as above. In the states as above.	end of double-ended new invert diluent bottle over dly insert free end of stopper at its centre. w in diluent.	er the
	6.	bot: rot: that	tle st ate co t conc	opper. Shake ncentrate bott entrate is cor	vigorously for the until all m	g needle from concentrat 5 seconds, then agitate aterial is dissolved. .ved; otherwise, active r.	e or Be sure
	NOT	E:	Do n	ot refrigerate	e after reconst	itution.	
			Do n	ot use if a ge	el forms on rec	constitution.	
	Rat	e of .	Admini	stration			
- 	or rat Acc mor	more a es: i ording e AHF	AHF un .e., a gly, t units	its per ml mus maximum admin he administrat per ml must l	st be administenistration rate tion of a 30-ml be evenly regul	man), HEMOFIL T, contain red at carefully control of 2 ml per minute. total volume containing ated over a period of 1 g less than 34 AHF units	lled g 34 or 5 or
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-			dyn far yn yn my armef an o chwar yn mae yn a far a chwar an fr				
	1 <u>0</u>	can be given rap with no signific	•		0 ml over a 3-minute period	>	
		rate before and	during admini rease of pulse	station of th rate occur,	should determine the pulse e AHF concentrate. Should reduce the rate of	a	

#### Administration: Use Aseptic Technique

Administration of Antihaemophilic Factor (Human), HEMOFIL T, should begin not more than 3 hours after reconstitution is complete.

The reconstituted material should be at room temperature during administration.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

- After reconstituting the concentrate as described under "Reconstitution", open the filter spike package by peeling back the label of the blister pack. (See Figure 1)
- 2. Hold the clear plastic blister pack at the rim of the filter spike and aseptically attach the filter spike to an empty plastic syringe. Twist the filter spike onto the syringe to ensure a secure connection. (See Figure 2)



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				· · ·							
	3.	Dra	w back	the plunger to	o admit air into	the syringe.					
	4.	bot pre	tle on vent s	a flat surface lipping, insert	e and while holdi	Factor (Human), HEMOFII ng the bottle firmly to ndicularly through the re 3)					
	5.				and then withdraw ge. (See Figure	the reconstituted 4)					
		•									
	6.				filter spike from ect intravenously	the syringe; attach a	1				
	r a single use. If the bottle of concentrate, into the same syringe he vein needle.										
	HOT	HOW SUPPLIED									
	HE	MOFIL	emophilic Factor (Human), Method Four, Dried, Heat-Treated, L T, is furnished with a suitable volume of Water for Injections . a double-ended needle, and a filter spike.								
The number of International Units of AHF activity, as determined each lot is stated on the label of each bottle.											
	ST	STORAGE									
	HEI Fre	Antihaemophilic Factor (Human), Method four, Dried, Heat-Treated, HEMOFIL T, should be stored under ordinary refrigeration (2° to 8°C) Freezing should be avoided as breakage of the diluent bottle might occur.									
						y be stored for up to a store, not to exceed 2					
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	tion of Fa ence to t New Ha posium,	actor IX conce he P.P.S.B. fra emorrhagic S	ntrates with special refer- ction, in Hemophilia and tates. International Sym- The University of North		
	Physiolo	s KM, Penick ogic basis of lia. Arch Patho	GD, Langdell RD, et al: transfusion therapy in bl 61:6, 1956		
	3. Biggs R: treatmen 1957	Assay of antil t of haemophi	naemophilic globulin in the lic patients. Lancet 2:311,		
	for meas Factor V studies a Hemoph	uring minimum 'III applied in nd in detecting ilias. Brinkhou	I, Hiller MC: A new method in vivo concentrations of distribution and survival Factor VIII inhibitors, in The s KM (ed), Chapel Hill, The lina Press, 1964, p 29		
	Hemoph	ilias. Brinkhou	of clotting factors, in The s KM (ed), Chapel Hill, The lina Press, 1964, p 185	•	
	studies a	us KM: Hemo and the evoluti Clin Pathol 41:	philia-pathophysiologic on of transfusion therapy. 342, 1964		
	of infectiv	vity of hepatitis	Thomas W, et al: Reduction B virus and a non-A, non-B treatment of human anti-		
• •	Abstract Sympos	s, 2nd Interna	<li>(F) concentrates. Short tional Max v. Pettenkofer lepatitis, Munich, October published.)</li>		
	new high philic fa classical	t potency glyc ctor (AHF) ci	m E, Roberts HR, et al: A ine-precipitated antihemo- precentrate: Treatment of hemophilia with inhibitors.		· · ·
(	Treatmer	nt of hemophili	e JV, Corrigan JJ, et al: a with glycine-precipitated Med 275:471, 1966	· ·	
	10. Shanbroi of severe	m E. Thelin GM	l: Experimental prophylaxis h a Factor VIII concentrate.		
	Manager	ment of Hem	c care, in Comprehensive ophilia. Boone DC (ed), Co., 1976, p 2		
	12. Hilgartne Littletor, 1976, p 1	Mass., Publis	Hemophilia in Children. hing Sciences Group, Inc.	, .	a stational Anna anna anna Anna anna
	VIII dosis controlle	s in prophylaxis	P, Zimmermann K: Factor of hemophilia A; A further c Xith Cong W.F.H. Tokyo, p 363	· .	
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# APPENDIX IV

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# PROPOSED TEXT FOR DATA SHEET

דום	ION		PAGE	of 5	SUPERSEDES		LIST NO. BASIC	PART NO	· ·	RE
	тот	AL COPIES		ITEM	DATA SHEET	ATA SHEET STOCK				
20	PRO	DUCT ANT	IHAEMOPH	ILIC F	ACTOR (HUMAN	N),HEAT	TREATED		<u> </u>	
					<u></u>		STYLE		<u>1999 - Barrow Brows - Barrow Barrow Barrow Barrow</u>	
CAL	PRIN	ITED SIZE	<u></u>			TOLER	ANCES		an a	
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		DATA SHE	ET				LOGO TRAVENOL			
			ANTIHAEM	OPHILI	C FACTOR (HI	UMAN)				• •
	Method Four, Drie				ried - Heat	Treate	ed			
			HEMOFIL	T						
AHIWUHK			Presenta	tion:	HEMOFIL antihaemo concentra plasma.	T, is a ophilic ated fo The pr (0.010	c Factor (Human) a sterile, Stable factor (Factor orm. It is prepa roduct also conta mg) or less per ng agent.	e, dried pr VIII, AHF, ared from f ains a trac	eparation of AHG) in resh-frozen hu e amount of hu	uman epari
	• Antihaemophilic Fa					th relatively sma Each lot is as	all amounts ssayed and	of fibrinogen labelled for	n and its	
د						The use of Antihaemophilic Factor (Human), HEMOFIL T, is indicated in haemophilia A (classical haemophilia) for the prevention and control of haemormagic episodes.				
•	The concentrate can patients with acqui exceeding 10 Bethes the dosage should b determinations of c					acquired Factor N ethesda Units per Ald be controlled	/III inhibi r ml. Howe d by freque	tors not ver, in such u nt laboratory		
		·			Antihaemo Willebrar	ophilic nd's di	: Factor (Human) sease.	is not ind	icated in von	
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ITEM						
PRODUCT	<u>.</u>					
		·	an a			
Dos	age an	<u>ıd Adm</u> i	Method Four, with the num being define	Dried, Heat-Tr ber of AHF unit d as the activi	Antihaemophilic Factor eated, HEMOFIL T, is la s which it contains, l ty present in 1 ml of r an 1 hour old (100% AH	abelled AHF unit normal
			per kg body 2% (of norma to 4.0 units in AHF level to 14 years adults.) Th calculate, a	weight consiste 1), while Shanb per kg. produc . (The former of age, while t e following for pproximately, t	that infusion of 1 uni- ntly produces an increa- rom and Thelin found the an increase of 10% ( authors worked with boy he latter worked prima- nulae can therefore be he expected response f or a given effect:	ase of hat 3.8 of normal) ys 8 months rily with used to
			I. Units re	equired = Body desir	weight (in kg) x 0.4 x ed AHF increase (in %	of normal)
			II. Expected	l AHF increase (	in % of normal)=	
•				lministered ght (in kg) x O	.4	
					al would call for a fa receding formulae.	ctor of
			haemostasis The amount o	varies with cir of factor to be	emophiliacrequires for cumstances and with th supplied will depend o the AHF level desired	e patient. n the
			generally su or more is a Factor VIII for optimum that the fin 80 to 100%, dose of Fact be given abo units of blo of concentra recovery roo	ubside with a si attained. For m level of 35 to clot formation. rst dose of Fact be given an hour tor VIII half th but 5 hours afte bod were lost du ate should be gi om. The Factor ninimum of at le	haemorrhagic episodes ngle infusion if a lev ore serious haemorrhag 50% if normal should b In surgery, Kasper r or VIII, to achieve a before the procedure. e size of the priming r the priming dose. I ring the operation, a ven when the patient r VIII level should be m east 30% for a healing	el of 30% es, a e obtained ecommends level of A second dose should f several third dose eaches the aintained

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				na fan fan de antifik en en fan gener pensjon fik en antifik fan ster fik fan ster fik fan fan fik fan ster			
				medical judgm condition of desired level Antihaemophil by the intrav	ment of the p patient, deg l of Factor V lic Factor (H venous route.	ns should be made based on the hysician regarding circumstand ree of deficiency, and the III to be achieved. uman) is to be administered or The material should be	æs,
بر ا				Injections Ph	n.Eur.	propriate volume of Water for philic Factor (Human), HEMOFII	

containing 34 or more AHF units per ml must be administered at carefully controlled rate: i.e. a maximum administration rate of 2 ml per minute.

AHF preparations containing less than 34 AHF units per ml can be given rapidly, at a rate of 10 to 20 ml over a 3-minute period, with no significant reactions.

As a precautionary measure, the physician should determine the pulse rate before and during administration of the AHF concentrate. Should a significant increase of pulse rate occur, reduce the rate of administration or discontinue.

#### CONTRAINDICATIONS

None known.

#### WARNINGS

This concentrate is prepared from large pools of fresh human plasma which may contain causative agents of viral hepatitis. However, each unit of plasma used in the manufacture of this product has been found to be nonreactive for hepatitis B surface antigen (HBsAg) when tested with licenced third generation reagents. In addition, this product has been subjected to a heating procedure during its manufacturing process designed to reduce the risk of transmission of hepatitis. Although these testing and heating steps reduce the risk of hepatitis transmission, the possibility of such transmission should be considered in use of the product.

#### PRECAUTIONS

#### General

This Antihaemophilic Factor (Human) preparation contains blood group

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PRODUC	Γ						
				antentitenteterennen an in er			
				nýše lým klana na spislova na podružno spislova podružna klana s			
	dos sur be a hae	es are gical monito matocr	needed care is red for it valu	d, as when in s involved, p r signs of in Jes. Haemoly	hibitors are pre atients of blood travascular haem tic anemia, when	rge or frequently repea sent or when pre and po groups A, B, and AB sh olysis and decreasing present, may be correc Red Blood Cells (Human)	st- ould ted

essential before the administration of Antihaemophilic Factor (Human) is initiated.

Since Antihaemophilic Factor (Human), Method Four, Heat-Treated, HEMOFIL T, contains small residual amounts of fibrinogen which tend to cause the ground surface of glass to stick, plastic (disposable) syringes should be used.

#### Laboratory Tests

Although dosage can be estimated by the calculations above. it is strongly recommended that whenever possible, appropriate laboratory tests be performed on the patient's plasma at suitable intervals to ensure that adequate AHF levels have been reached and are maintained.

If the AHF level fails to reach expected levels or if bleeding is not controlled after apparently adequate dosage, the presence of inhibitor should be suspected. By appropriate laboratory procedures, the presence of inhibitor can be demonstrated and quantified in terms of AHF units neutralised by each ml of plasma or by the total estimated plasma volume. After sufficient dosage to neutralise inhibitor, additional dosage produces predicted clinical response. It should be noted that when inhibitor is present, measurement of Lee-White clotting time may be a better index of adequacy or dosage than measurement of circulating AHF.

#### ADVERSE REACTIONS

Allergic reactions may be encountered from the use of AHF concentrate preparations.

#### Pharmaceutical Precautions

Antihaemophilic Factor (Human), Method Four, Dried, Heat-Treated, HEMOFIL T, should be stored under ordinary refrigeration ( $2^{\circ}$  to  $8^{\circ}$ C). Freezing should be avoided as breakage of the diluent bottle might occur.

Antihaemophilic Factor (Human), HEMOFIL T may be stored for up to 1 month within the dating period at room temperature, not to exceed 25°C.

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ITEM					
PRODUCT					
	1 Category				
Preso	cription Or	ly Medicine.			
Packa	age Quantit	ies			
is fu	urnished wi	: Factor (Huma ith a suitable edle, and a f	an), Method Four, Dr e volume of Water for filter spike.	ied, Heat-Treated, H r Injections Ph.Eur	HEMOFIL T . a
Unit	Size		Average Activity	Code	Number
30	0 m1 0 m1 0 m1		250 I.U./Vial 750 I.U./Vial 1050 I.U./Vial		0-610 0-630 0-639
Furtl	her Informa	tion			
Nil					
Produ PL01					
Produ	uct Licence	Number			
PLOT	16/				
Date	of Prepara	tion			
July	1984				
Thet	enol Labora ford, olk, ENGLAN	atories Ltd., ND.			
Tele	phone Thet	ford (0842) 4	581		
	an a	DATE	QUALITY ASSURANCE	DAT	E

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PACKAGE DEVELOPMENT

Section Page Number PART IV - STUDIES IN HUMANS 1 1. Human Pharmacological Studies 1.1 Half life and recovery 1.2 Neoantigenicity 8 Clinical Trials 2. 8 3. Adverse Reactions 10 APPENDIX I HALF-LIFE AND PERCENT RECOVERY - CLINICAL : REPORT (DR. BLATT, NORTH CAROLINA, U.S.A.) APPENDIX II HALF-LIFE AND PERCENT RECOVERY - CLINICAL 39 : REPORT (DR. ALLAIN, PARIS, FRANCE) APPENDIX III 60 ASSAY OF CIRCULATING IMMUNE COMPLEXES IN : HAEMOPHILIAC PATIENTS (PROF. MASSON, BRUSSELS, BELGIUM) APPENDIX IV AN ATTEMPT TO REDUCE THE RISK OF HEPATITIS 67 : WITH HEAT TREATED FACTOR VIII CONCENTRATE -

MILAN, ITALY)

INTERIM REPORT (DR. COLOMBO AND PROF. MANNUCCI,

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(z)

#### 1. HUMAN PHARMACOLOGICAL STUDIES

Three human pharmacological studies have been performed. These were designed to demonstrate the lack of neoantigenicity and similarity of half life and recovery of Heat-treated AHF when compared with non heat-treated standard AHF.

#### 1.1 Half life and recovery

Haemophilia A is the inherited inability to manufacture the plasma protein known as Factor VIII or Antihaemophilic Factor (AHF). The disorder is inherited as a sex linked recessive characteristic. Patients with haemophilia are therefore males with low levels of AHF in their plasma. Clinically, such patients can be divided into groups who have severe manifestations (AHF <1% of the normal value), moderately severe (AHF = 1-5%), and mild (AHF = 5-20%) (1-2).

In addition to the above correlation between inherited blood level of AHF and severity of disease, it is generally accepted that the level of AHF attained in the patient's plasma following infusion of AHF correlates directly with the efficacy of the administered AHF. (3-5) The clinical studies reported here emphasise the blood levels of AHF achieved following infusion of Antihaemophilic Factor (Human, Method Four, Treated), when compared to the reference material (Antihaemophilic Factor, Human, Method Four, Non-Dextrose). These materials will be referred to subsequently as AHF Treated and AHF Reference respectively.

Two human clinical studies were conducted to demonstrate the safety and efficacy of AHF Treated by evaluating survival and recovery of the AHF.

#### a) <u>Half-life and Percentage Recovery-Clinical Report</u> from U.S.A.

In the U.S.A. six non-bleeding haemophilia A patients were each infused with both AHF Treated and AHF Reference (as a control). A nominal dosage of 50 AHF units/kg was employed.

A statistical comparison of the results (using the sign test) indicated no significant difference in the average or median half-lives for the two products, AHF Treated and AHF Reference (p=1.0000). The results are given in Table I.

A statistical comparison of the Factor VIII recovery was performed by measuring the Factor VIII levels in the patients blood during the post-infusion period and calculating the maximum Factor VIII activity as a percentage of the normal values. Using the sign test results indicated a nonsignificant difference in the average of median recoveries for the two products (p = 0.2188). The results are given in Table II.

The Clinical Report of the U.S. study is included as Appendix I.

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TABLE 1	
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# HALF-LIFE

	<u>Half-Lif</u>	fe Hours
Patient	AHF Treated	AHF Reference
JHM	8.3	12.6
JMS	8.5	6.6
ELB	7.0	8.8
GDM	8.1	7.8
RWL	7.2	8.2
CWC	8.3	7.6
Average	7.9	8.6
Median	8.2	8.0

# TABLE II

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# RECOVERY

# (Maximum % of Normal Over the Post-Infusion Period)

	Recover	<u>y (%</u> )
Patient	AHF Treated	AHF Reference
JHM	53%	88%
JMS	92%	114%
ELB	75%	81%
GDM	77%	87%
RWL	127%	107%
CWC	60%	80%
Average	80.7%	92.8%
Median	76%	87.5%

#### b) <u>Half-life and Percentage Recovery - Clinical Report</u> from France

In France six regularly bleeding (>1 bleed per month) Haemophilia A patients were each infused initially with AHF Reference as a control, followed by three injections of AHF Treated for the treatment of spontaneous bleeding as warranted by their clinical condition.

The patients were treated with both materials and were judged on the basis of clinical reponse to have been treated effectively. The effectiveness of treatment was also evaluated by comparing the Factor VIII:c plasma level attained with the AHF Treated concentrate when compared to the plasma level attained with AHF Reference in the same haemophilic individual. The comparison was made in order to allow for individual patient variation. The results of the Factor VIII recovery and half-life are summarised in Table III. The recovery and half-life values show that the AHF Treated and AHF Reference were not distinguishable. No untoward side effects were observed.

The equivalence of Hemofil T concentrate and Hemofil concentrate with regard to recovery and biological half-life support the contention that the two products are therapeutically equivalent.

#### TABLE III

#### IN VIVO RECOVERY AND HALF-LIFE OF AHT HTV VERSUS CONTROL

	F REFERENCE 800401AH11	AHF TREATED Lot 2750T001	AHF REFERENCE Lot 800401AH11	AHF TREATED Lot 2750T001
J.P.S.	8.5	8.5	96.7	91
A.F.	8.5	7	(>80)*	83
R.B.	11.5	10.5	102	105
К.К.	10.5	10	102	98
N.K.	11	8.5	100	105
J.P.B.	11	11	94	89
			* no data availa	able after 1 hr.
mean	10.2	9.3	mean 95.7	95.2
standard deviation	1.3	1.5	standard 8.34 deviation	8.99
student tes	tt1		student test t	.12

F.VIII HALF-LIFE, (hours)

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IN VIVO F.VIII :c RECOVERY (%)

In addition, no inhibitors or neoantigens were formed, as evidenced by half-life and percent recovery data summarised below in Table IV for first vs. third injections where no difference is apparent between doses.

These results lend further support to the conclusion that the heat-treatment process has not significantly altered the structure of the Factor VIII.

#### TABLE IV

IN VIVO RECOVERY AND HALF-LIFE OF AHF-TREATED, FIRST VERSUS THIRD INJECTIONS

	F.VIII Half-	Life (hours)	In Vivo F.VIII:	c Recovery (%)
PATIENT	AHF-Treated LOT 2570T001 First Injection	AHF-Treated LOT 2570T001 Third Injection	AHF-Treated LOT 2570T001 First Injection	AHF-Treated LOT 2570T001 Third Injection
2 A.F.	7	7	83	95
4 K.K.	10	8	98	98

The clinical report of the French study is included as Appendix II.

#### CONCLUSION

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AHF Treated has been shown to be therapeutically equivalent to AHF Reference, and was well tolerated. There were no adverse reactions. The dose used was considered appropriate for treating mild bleeding episodes, but higher doses might be necessary for more major bleeding. The contraindications are the same as those for AHF preparations currently in use.

#### 1.2 Neoantigenicity

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#### Assay of Circulating Immune Complexes in Haemophiliac Patients

The six patients treated in the above study (1.1.b) were also used for measurement of circulating immune complexes. Immune complexes were measured before the first and after the third infusion of AHF Treated. The immune complex levels were determined by two tests based on inhibition of latex agglutination using either rheumatoid factor or murine agglutinator.

In conclusion it was confirmed that haemophiliac patients have higher levels of circulating immune complexes than the normal population. However, no significant increase was noted in immune complex levels after three infusions of AHF Treated.

The results are summarised in Table V.

The full report of this study is included as Appendix III.

# TABLE V

### LEVELS OF CIRCULATING IMMUNE COMPLEXES

PATIENT	TEST	TIME OF SAMPLING			
		Before Untreated AHF	10-15 Days After Untreated AHF	10-15 Days After Ist AHF Treated	10-15 Days After 3rd AHF Treated
AF	* RF	25	22	24	27
	MAG	340	340	340	370
KK	RF	25	27	25	30
	MAG	275	325	290	280
JPS	RF	38	38	37	45
	MAG	325	350	310	270
RB	RF	42	44	41	47
	MAG	315	360	360	375
JPB	RF	32	30	30	32
	MAG	275	275	300	315
KN	RF	26	26	-	26
	MAG	190	180	-	220

\* Tests as follows:

RF - Rheumatoid Factor (in equivalents of heat aggregated IgG ( $\mu$ g/ml)

MAG -

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Murine Agglutinator (in equivalents of heat aggregated

IgG (µg/ml)

**REFERENCES:** 

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#### 2. CLINICAL TRIALS

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A clinical study to assess the degree of reduction of hepatitis risk transmission afforded by heat treatment of Factor VIII is currently ongoing.

A study is being performed on a multicentre basis under CTX0116/0137A and is prospective and non-comparative. Previously untreated ("virgin") haemophiliacs both vaccinated and nonvaccinated against hepatitis B, received AHF-Treated following a first bleed and for each subsequent haemorrhage.

Beginning in December 1982, 34 patients from 10 centres in 5 countries were enrolled into the AHF-Treated studies. However, 12 patients have had to be excluded from the analysis because they did not meet the selection criteria (the majority having been treated with blood or blood products and therefore not "virgin"). Currently 22 patients are being evaluated prospectively, of whom 20 have been followed for enough time (at least 3 months) to provide preliminary data on the safety and efficacy of AHF-Treated.

In summary, 11 of the 20 patients (55%) treated with AHF-Treated developed post transfusion hepatitis (PTH). One patient developed cytomegalovirus infection. However, this was considered to be unrelated to the treatment as the same lot of AHF-Treated was given to another 6 patients without transmitting CMV infection. One patient had elevated transaminases briefly, but this was not interpreted as being due to hepatitis. In 7 patients no symptoms of hepatitis were noted.

Hepatitis in the 11 patients was always of the Non A, Non B type of a moderate severity and anicteric in all but one case. No cases of seroconversion for Hepatitis B have occurred although only 6 of the 20 patients had been vaccinated against hepatitis B. The efficacy and tolerance of AHF-Treated was equal, in all cases, to that recorded for standard AHF.

A copy of the interim report is included as Appendix IV.

#### 3. ADVERSE REACTIONS

The product Hemofil-T (Antihaemophilic Factor (Human) Method Four Heat Treated) has been used widely since early 1983. To date over 4,000 patients have been treated with Hemofil-T (based on sales figures and the annual Factor VIII requirement of a severe Haemophilia A patient). A total of 8 adverse reactions have been reported and these are detailed below.

The total number of units of AHF-Treated sold in Europe (including West Germany, Spain, Sweden and Belgium) and the U.S.A. is as follows:

	HEMOFIL-T USA	GE (Millions of I.U.)	
Year	<u>U.S.A.</u>	Europe	Total
1983	46.7	41.5	88.2
1984 (7 months)	41.6	60.6	102.2
	88.3	102.1	190.4

The complete number of adverse reaction complaints reported to Travenol Laboratories is as follows:

REPORTS FROM THE U.S.A.

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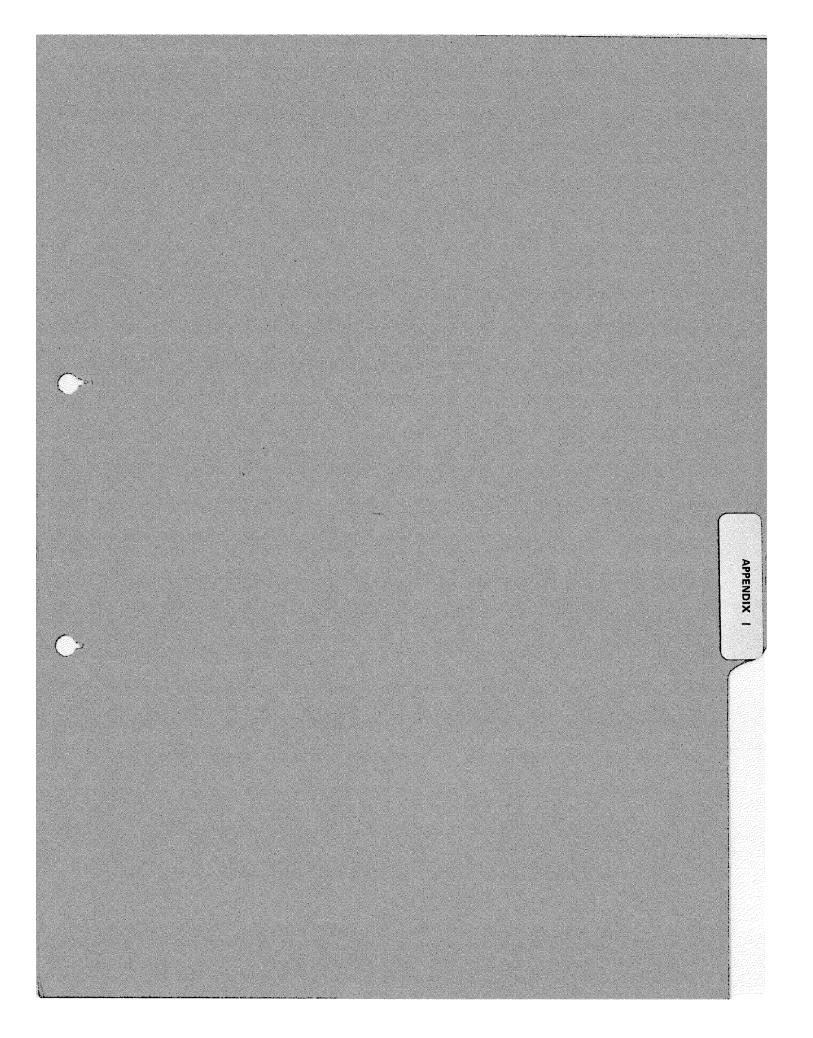
Date	Lot No.	Adverse Reactions
17.7.84	2792X370AA	Hepatitis A
2.5.84	2792X358AB	Non-A, Non-B Hepatitis
20.3.84	2792X371AA	Non-A, Non-B Hepatitis
13.1.84	2792X301AB 2792X331AB	Chest discomfort, hard breathing, rapid heart rate. After steroid administration-hypotension
22.12.83	2792X358AB 2792X371AA	Non-A, Non-B Hepatitis

#### REPORTS FROM EUROPE

16.8.84	Not Available	Non-A, Non-B Hepatitis
16.4.84	831108AH12A 830207A320A 830308AH11A	Anaphylactic reations occurred in two patients - however, all lots were used in other patients without adverse reactions being reported

In conclusion the reported rate of adverse reactions is low and the reactions noted have been confined to non-A, non-B hepatitis, which is a common condition in haemophilic patients on Factor VIII therapy, one case of hepatitis A (probably not product related) and three anaphylactic reactions. The latter cases involved lots of product used in other patients without complaint and the reaction is probably patient specific.

The adverse reactions reported are characteristic of those found when using coagulation factors prepared from human plasma.



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# APPENDIX I

# HALF-LIFE AND PERCENT RECOVERY -

# CLINICAL REPORT (DR. BLATT, NORTH CAROLINA, U.S.A.)

# Antihemophilic Factor (Human), Method Four, Heat Treated

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Half-life and Percent Recovery Clinical Report The following is a summary of the half-life and recovery data for Antihemophilic Factor (Human), Method Four, Heat Treated (Hemofil-T) from Dr. Philip Blatt of the University of North Carolina. Six (6) patients were involved, each of whom were infused with both Antihemophilic Factor (Human), Method Four, Heat Treated and identical material nonheated (Hemofil), as a control. A nominal dosage of 50 u/kg was employed. (Actually, the average dosages for the two products were 54.4 u/kg and 47.9 u/kg for Hemofil and Hemofil-T respectively). The detailed analyses are attached.

	<u>Half-lif</u>	e (hrs.)
Patient	Hemofil-T	Hemofil
JHM	8.3	12.6*
JMS	8.5	6.6
ELB	7.0	8.8
GDM	8.1	7.8
RWL	7.2	8.2
CWC	8.3	7.6
Average	7.9	8.6
Median	8.2	8.0

I. Half-life

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\*There is reason to suspect this result given the recovery curve and the half-lives for the other infusions.

A statistical comparison of the results (using a nonparametric procedure known as the sign test because of the small sample size and uncertainty surrounding the distribution of half-lives) indicated a nonsignificant difference in the average or median half-lives for the two products (p = 1.0000).

	Recovery (%)		
Patient	Hemofil-T	Hemofil	
JHM	53%	88%	
JMS	92%	114%	
ELB	75%	81%	
GDM	77%	87%	
RWL	127%	107%	
CWC	60%	80%	
Average	80.7%	92.8%	
Median	76%	87.5%	

## II. Recovery (maximum % of normal over the post-infusion period)

A statistical comparison of the results (again using the sign test) indicated a nonsignificant difference in the average or median recoveries for the two products (p = 0.2188).

In summary, there is no evidence to suggest that the two products differ with respect to half-life or recovery. (We should note, though, that the small sample size precludes the possibility of making a much stronger statement about the nonsignificant differences).

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Attachments

# HEMOFIL®-T TRIAL

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JHM 3450 u (50.7 u/kg) HEMOFIL

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For this set of data, 2 periods appear to be evident so we employ a 2-period changeover model.

Estimated change-over point is ~ 1 hr.

(1) Equation for 1st hr:

(x)	(y)
time (hr)	recovery (%)
.25	88
1	71
$\frac{y-88}{x25} = \frac{71-88}{125}$	<u>3</u> = -22.ō
y = 93.7-2	22.7x

(2) Equation for beyond 1st hr.

x(hr)	y(recovery)	
1 3 6 9 12	71 61 55 50 36	a = 72.4289 b = -2.8756 r =981 (p<.0025)

y = 72.4289 - 2.8756x

half-life =  $\frac{-a}{2b}$  = 12.6 hr.

Aside:  
Check on change-over point  

$$\hat{\gamma} = -\left(\hat{\alpha}_1 - \hat{\alpha}_2 \\ \hat{\beta}_1 - \hat{\beta}_2\right) = 1.1 \text{ hr.}$$
  
(reasonably close to 1 hr.)

JHM 3030 u (44.6 u/kg) HEMOFIL®-T

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For this set of data, there are two periods. However, there appears to be an <u>increase</u> in activity in the first hour, which is an anomaly. For purposes of analysis, a two-period changeover model will be used.

Estimated change-over point - 1 hr.

(1) Equation for 1st hr:

(x) time (hr)	(y) <u>recovery (%</u> )
.25	49
1	53

$$\frac{y-49}{x-.25} = \frac{53-49}{1-.25} = 5.3$$

$$y = 47.7 + 5.3x$$

(2) Equation for beyond 1st hr.

x(hr)	y(recovery)	
1 3 6 9 12	53 39 34 21 16	a = 52.71066 b = -3.24365 r =977 (p<.0025)

y = 52.71066 - 3.24365xhalf-life =  $\frac{-a}{2b}$  = 8.1 hr.

Aside: Check on change-over point
$\hat{\gamma} = -\left(\frac{\hat{\alpha}_1 - \hat{\alpha}_2}{\hat{\beta}_1 - \hat{\beta}_2}\right) = 0.6 \text{ hr.}$
(-1 -2)

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The revised change-over point suggests that perhaps there is only 1 period here and all data should be included (actually the value for 15 minutes is abnormally low, but we have no way of correcting for this).

(3) Equation for 15 minutes and beyond.

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a = 51.5359

b = -3.11089

$$r = -.979 (p < .0025)$$

y = 51.5359 - 3.11089x

half-life = 
$$\frac{-a}{2b}$$
 = 8.3 hr.

So the half-life has not been altered considerably by the change to a one-phase model.

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JMS 4600 u (53.8 u/kg) HEMOFIL®

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For this set of data, the recovery results at 15 minutes and 1 hour do not fit in with the remainder of the points. The slow fall-off period begins with the 3 hour result and the corresponding regression line is estimated from these data. The points at 15 minutes and 1 hour are discarded.

(1) Equation for 3rd hr. and beyond.

(x) time (hr)	(y) recovery (%)
3 6 9 12	48 27 17 8
a = 57	
b = -4	
r =	977 (p<.025)

y = 57.5 - 4.3x

half-life =  $\frac{a}{2b}$  = 6.6 hr.

JMS 4040 u (47.5 u/kg) HEMOFIL®-T

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For this set of data, the two phase model appears to be suitable. Estimated change-over point  $\approx$  1 hr.

(1) Equation for 1st hr.

 $\frac{y-92}{x-.25} = \frac{79-92}{1-.25} = -17.3$ 

$$y = 96.3 - 17.3x$$

(2) Equation for beyond 1st hr.

x(hr)	y(recovery)	
1 3 6 9 12	79 73 63 32 28	a = 86.86548 b = -5.13959 r =968 (p<.005)

y = 86.86548-5.13959xhalf-life =  $\frac{-a}{2b}$  = 8.5 hr.

Aside: Check on change-over point
$\hat{\gamma} = -\left(\frac{\hat{\alpha}_1 - \hat{\alpha}_2}{\hat{\beta}_1 - \hat{\beta}_2}\right) = 0.78 \text{ hr.}$
(reasonably close to 1 hr.)

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ELB 2300 units (60.2 u/kg) HEMOFIL®

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For this set of data, the two phase model appears to be suitable. Estimated change-over point = 1 hr.

(1) Equation for 1st hr.

'x	y
time (hr)	recovery (%)
.25	81
1	65

$$\frac{y-81}{x-.25} = \frac{65-81}{1-.25} = -21.\overline{3}$$

(2) Equation for beyond 1st hr.

x(hr)	y(recovery)	
1	65	
3	63	a = 71.15736
6 9	45 35	b = -4.02538
12	23	r =991 (p<.0025)

y = 71.15736 - 4.02538x

half-life =  $\frac{-a}{2b}$  = 8.8 hr.

Aside: Check on change-over point  $\hat{\gamma} = -\left(\frac{\hat{\alpha}_1 - \hat{\alpha}_2}{\hat{\beta}_1 - \hat{\beta}_2}\right) = 0.88 \text{ hr.}$ (reasonably close to 1 hr.)

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ELB 2020 units (52.9 u/kg) HEMOFIL®-T

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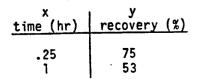
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For this set of data, the two phase model appears to be suitable. Estimated change-over point  $\approx$  1 hr.

(1) Equation for 1st hr.



$$\frac{y-75}{x-.25} = \frac{53-75}{1-.25} = -24$$

y = 81 - 24x

(2) Equation for beyond 1st hr.

x(hr)	y(recovery)	
1 3 6 9 12	53 47 38 16 10	a = 58.82741 b = -4.19797 r = -0.982 (p<.0025)

y = 58.82741-4.19797x

half-life =  $\frac{-a}{2b}$  = 7.0 hr.

Aside: Check on change-over point
$\hat{\gamma} = -\left(\frac{\hat{\alpha}_1 - \hat{\alpha}_2}{\hat{\beta}_1 - \hat{\beta}_2}\right) = 1.1 \text{ hr.}$
(reasonably close to 1 hr.)

GDM 3450 units (55.6 u/kg) HE MO FIL®

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For this set of data, because of the anomalous agreement in results for 15 minutes and 1 hour, only one period is considered (> 1 hr). (Note that the value for 12 hr. is probably too high, but it is more difficult to determine a course of action for that point; therefore, it is left alone).

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(1) Equation for beyond 1st hr.

x time (hr)	y recovery (۲)	
1 3 6 9 12	87 60 41 29 28	a = 81.1802 b = -5.19036 r = -0.927 (p<.025)

y = 81.1802-5.19036x

half-life =  $\frac{-a}{2b}$  = 7.8 hr.

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GDM 3030 units (48.9 u/kg) HEMOFIL®-T

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For this set of data there appears to be only one phase. Therefore, all data are combined for the analysis.

(1) Equation for 15 min. and beyond.

x time (hr)	y recovery (%)	
.25 1 3 6 9 12	77 67 48 36 33 22	a = 69.61104 b = -4.30932 r = -0.947 (p<.0025)

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y = 69.61104 - 4.30932x

half-life = 
$$\frac{-a}{2b}$$
 = 8.1 hr.

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RWL 4600 units (52.3 u/kg) HEMOFIL®

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For this set of data, the two phase model appears to be suitable. Estimated change-over point  $\approx 1$  hr.

(1) Equation for 1st hr.

x	y
time (hr)	recovery (%)
.25 1	107

 $\frac{y-107}{x-.25} = \frac{83-107}{1-.25} = -32$ 

$$y = 115 - 32x$$

(2) Equation for beyond 1st hr.

y = 82.4517 - 5.04061x

half-life =  $\frac{-a}{2b}$  = 8.2 hr.

Aside: Check on change-over point  $\hat{\gamma} = -\left(\frac{\hat{\alpha}_1 - \hat{\alpha}_2}{\hat{\beta}_1 - \hat{\beta}_2}\right) = 1.2 \text{ hr.}$ (reasonably close to 1 hr.)

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RWL 4040 units (45.9 u/kg) HEMOFIL®-T

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For this set of data, there are two periods. However, there is an anomalous increase in recovery values for the first hour. If we look at the data for 3 hours and beyond, the slow fall-off is evident. Therefore, only those data are considered.

(1) Equation for 3 hr. and beyond.

y = 82.5 - 5.73xhalf-life =  $\frac{-a}{2b}$  = 7.2 hr.

CWC 4600 units (53.8 u/kg) HEMOFIL®

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For this set of data, the rapid initial fall-off is not very noticeable. Therefore, all data are combined for the analysis.

(1) Equation for 15 min. and beyond.

y = 73.55295-4.84217xhalf-life =  $\frac{-a}{2b}$  = 7.6 hr. -12-

# CWC 4040 units (47.5 u/kg) HEMOFIL®-T

For this set of data, the rapid initial fall-off is not very noticeable. Therefore, all data are considered for the analysis.

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(1) Equation for 15 min. and beyond.

$$y = 57.15062 - 3.45292x$$

half-life = 
$$\frac{-a}{2b}$$
 = 8.3 hr.

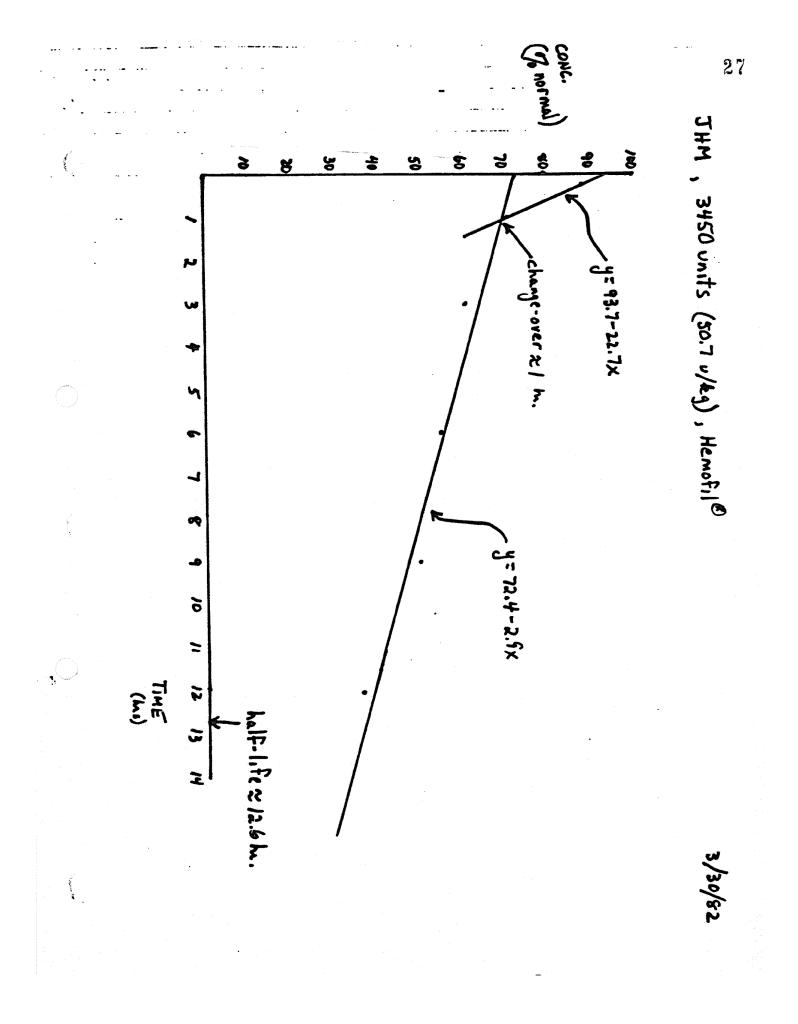
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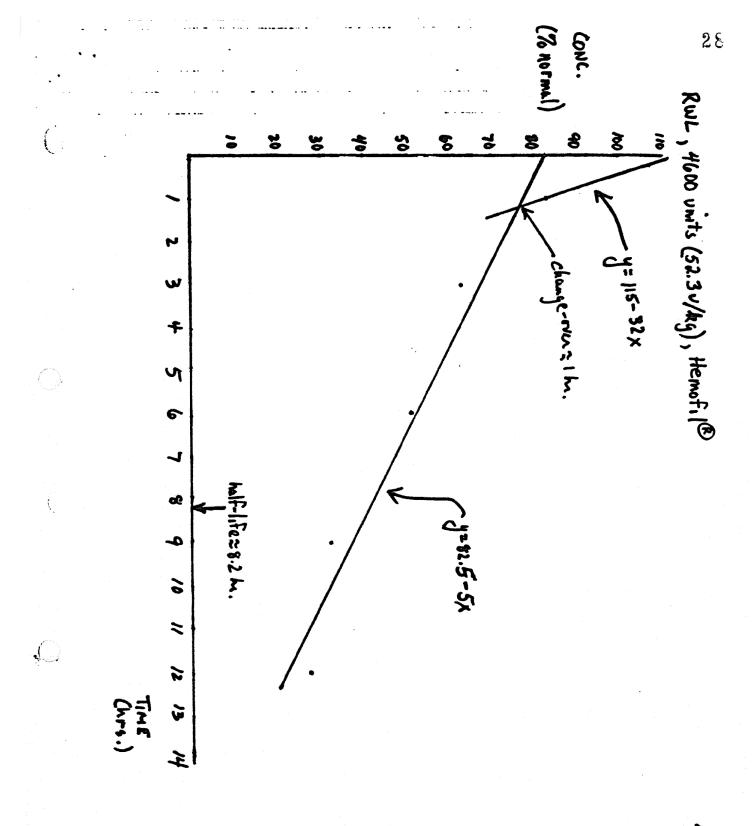
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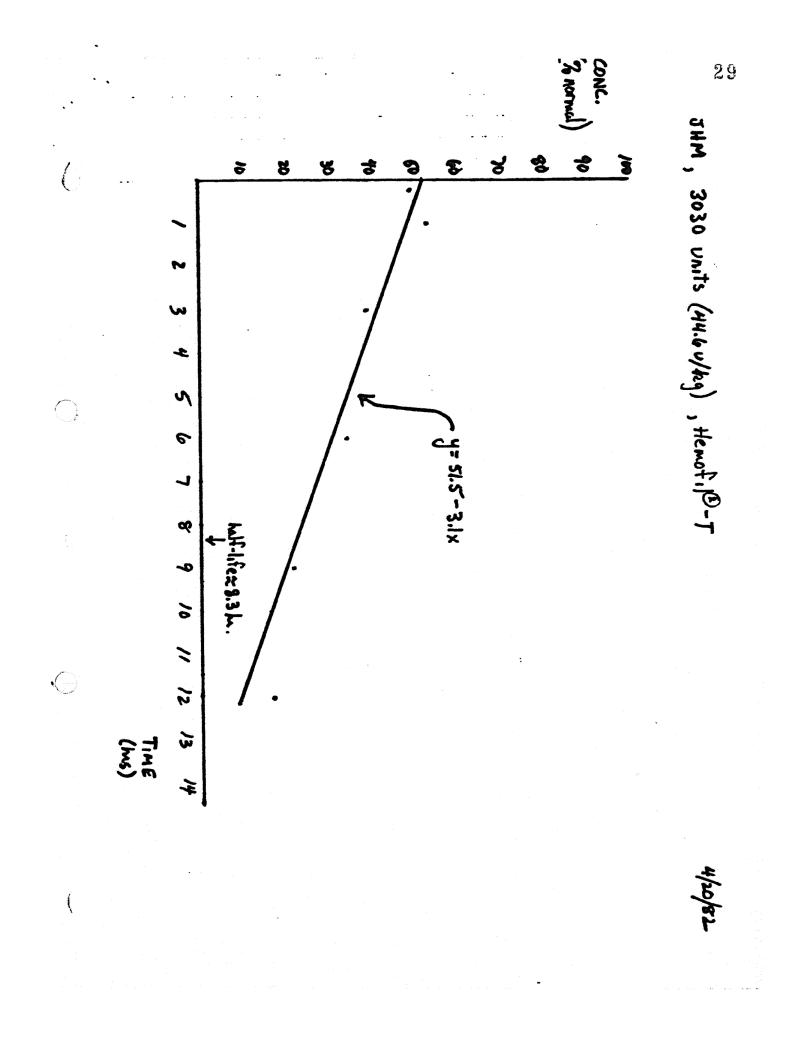
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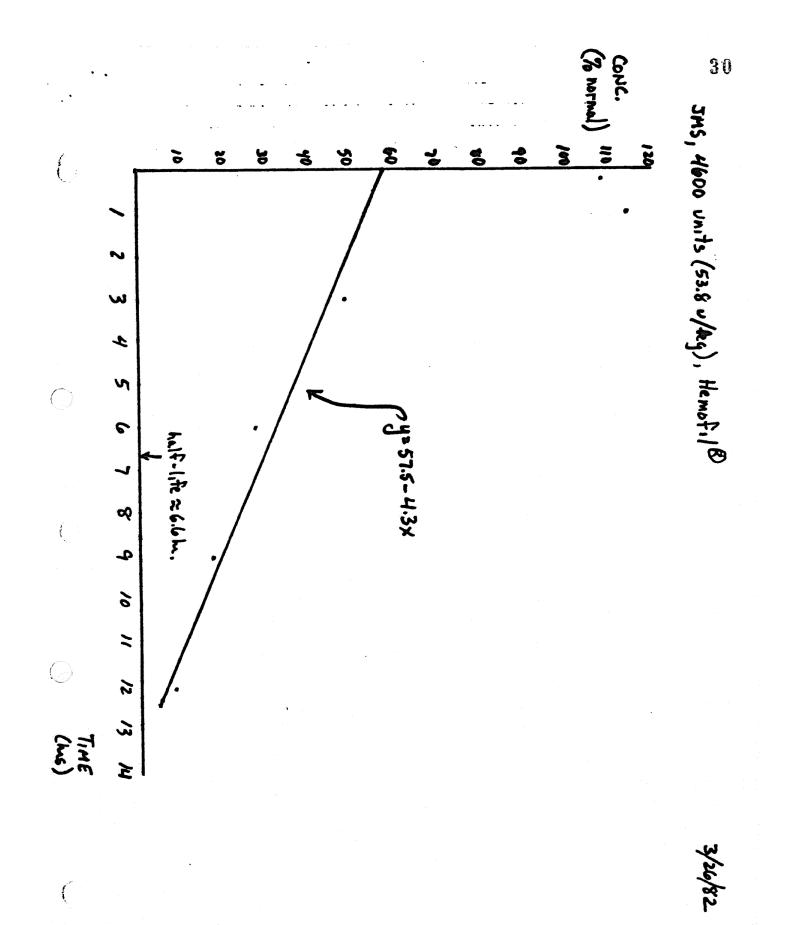
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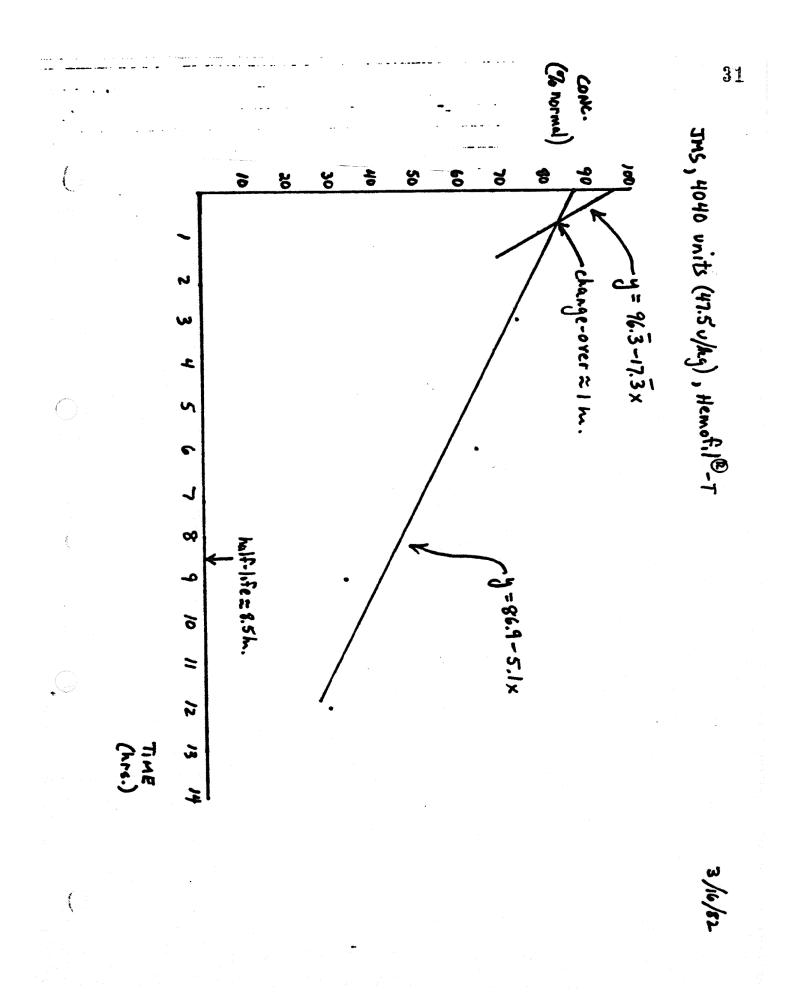


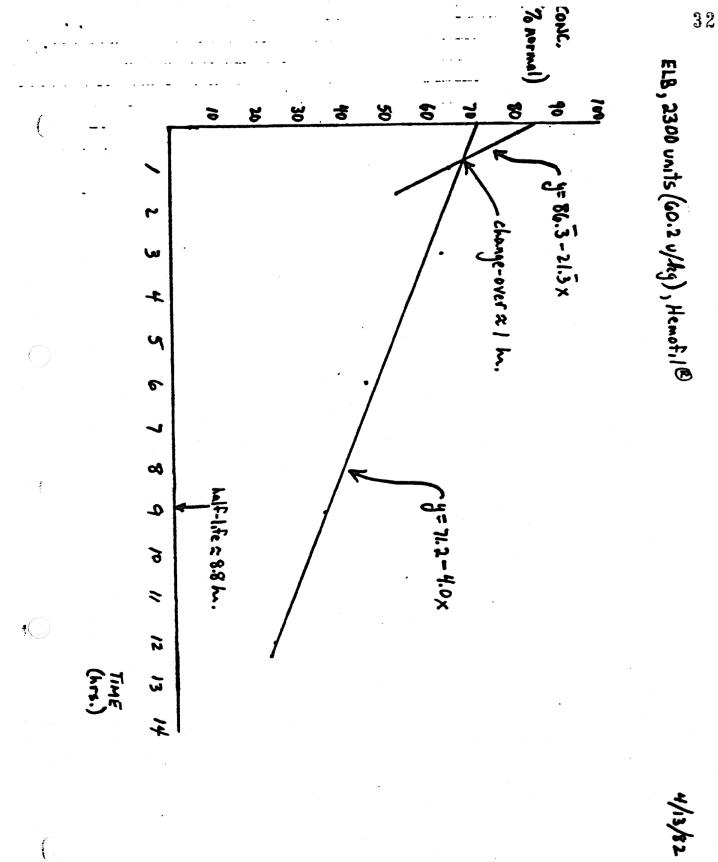


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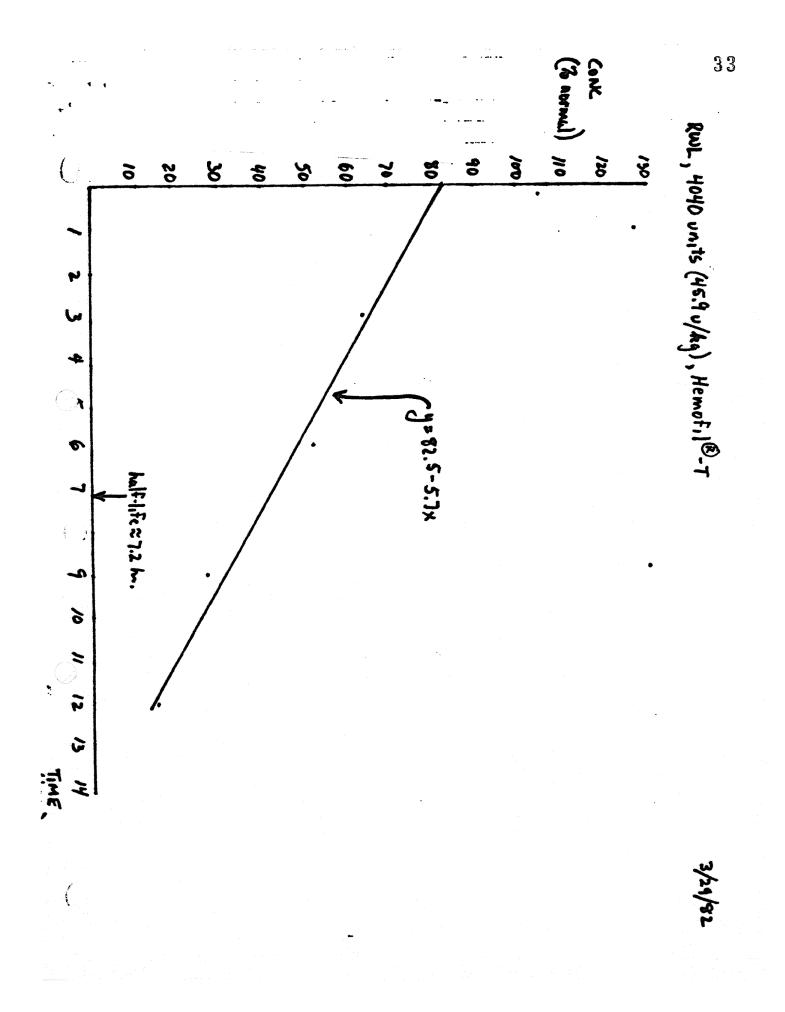


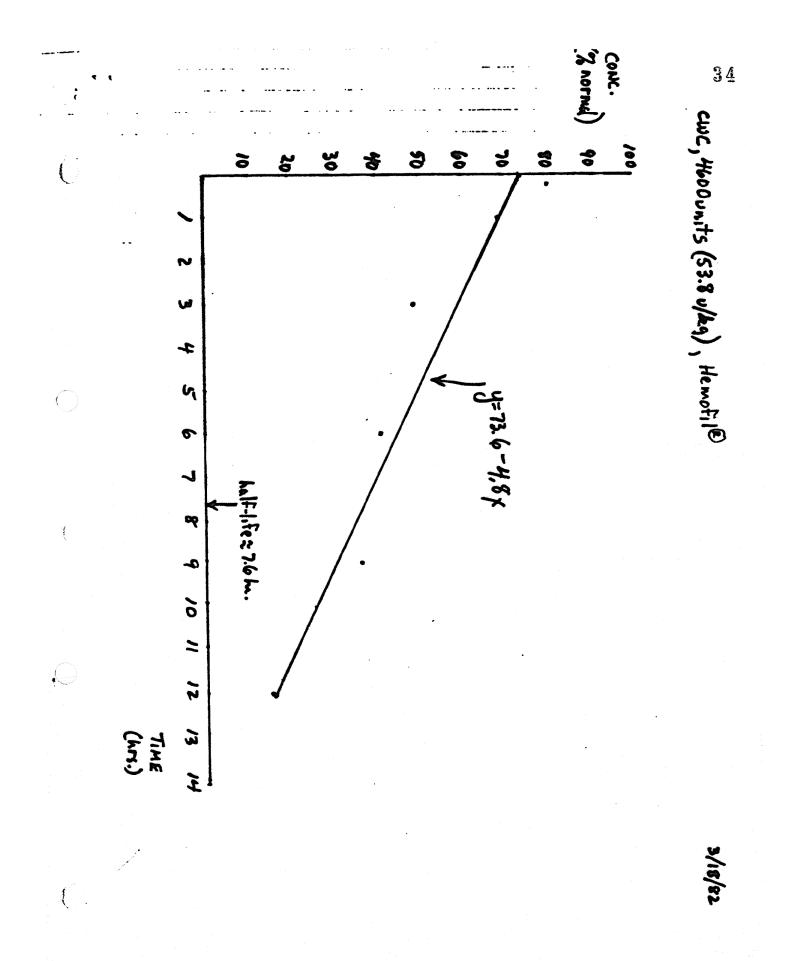


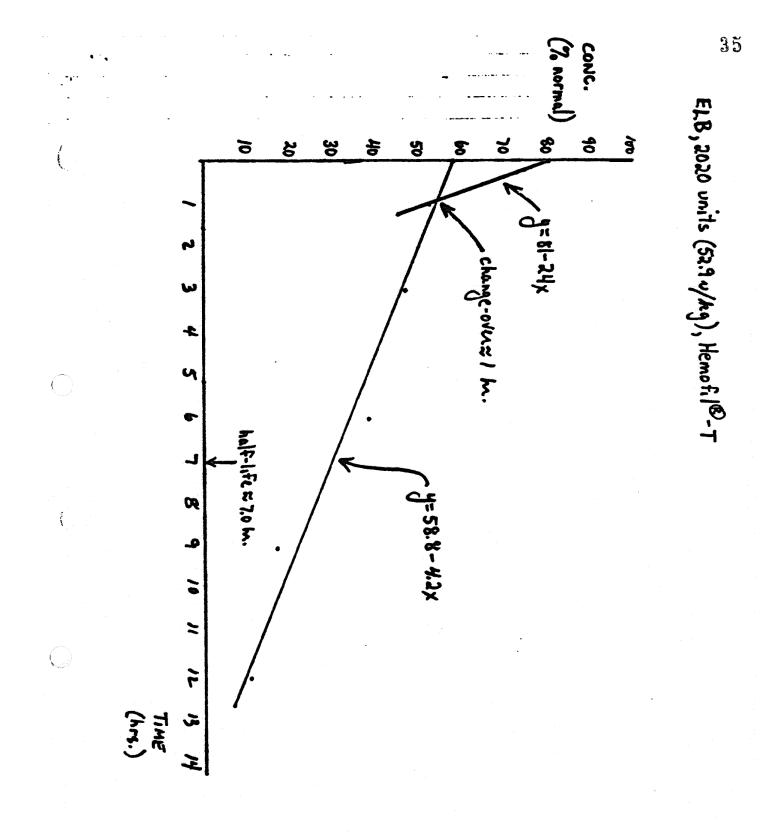




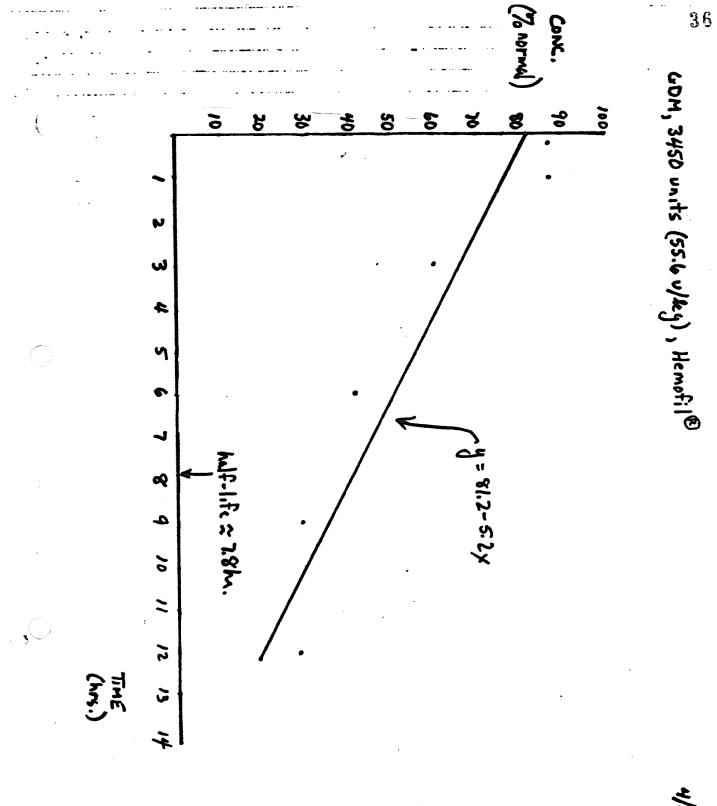
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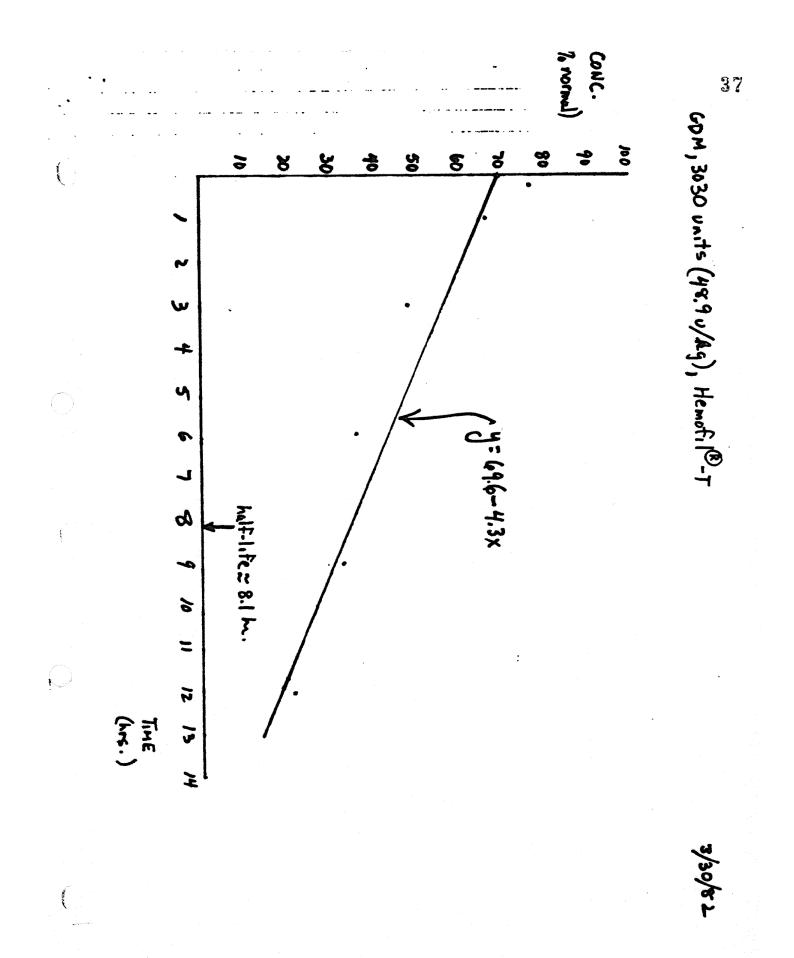


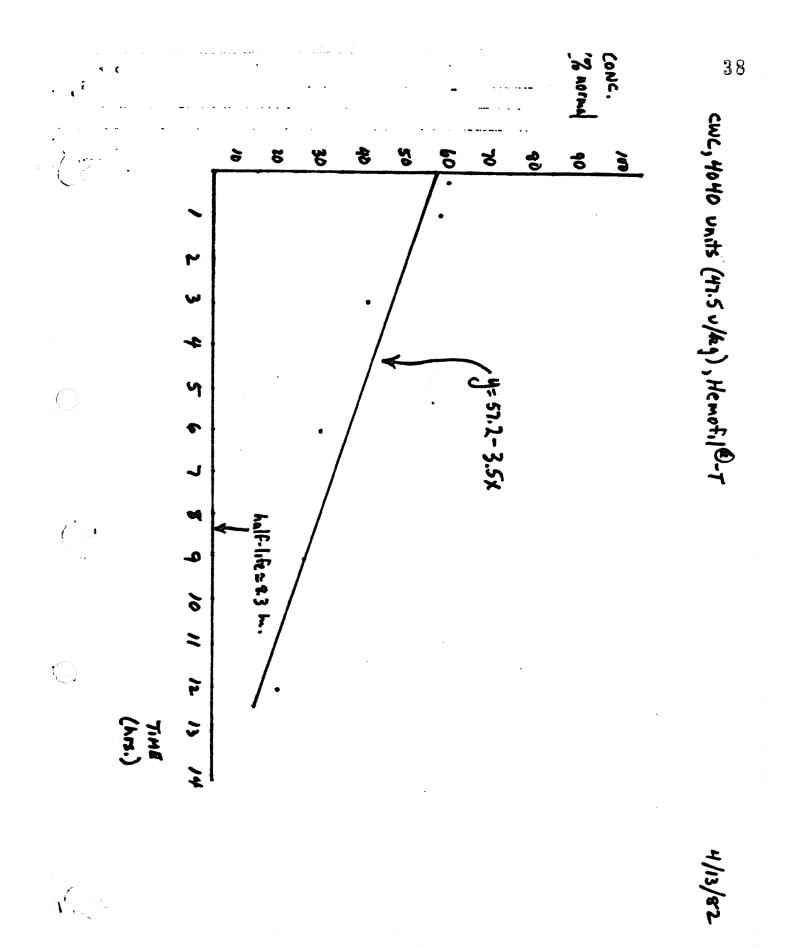
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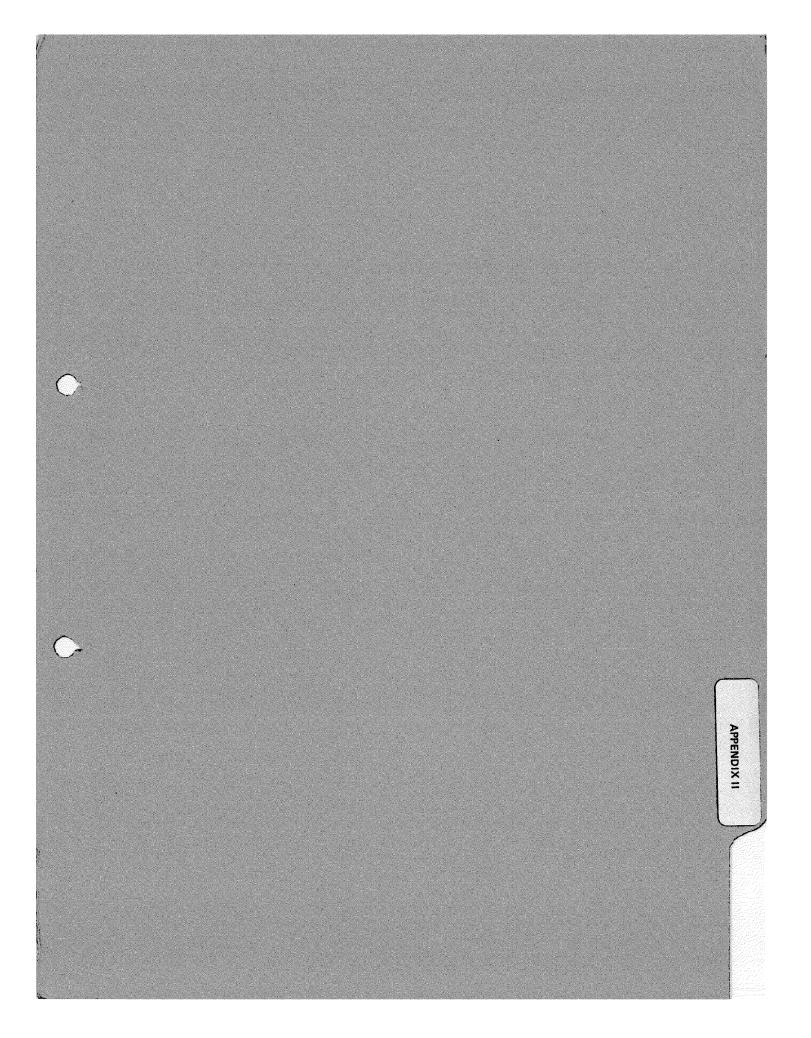


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## APPENDIX II

# HALF-LIFE AND PERCENT RECOVERY -

CLINICAL REPORT (DR. ALLAIN, PARIS, FRANCE)

#### TO WHOM IT MAY CONCERN

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# Summary

A clinical and biological evaluation of Factor VIII concentrate lot n° 800401 AH 11B was done. This lot was divided in two parts. Part 1 (NT) was infused first and part 2 (T) was infused second in each of the 6 patients involved in the study. The clinical tolerance of both parts was excellent and none of the patient suffered any side reaction. The clinical efficacy for 3 hemarthroses and 3 hematomas treated with NT, 4 hemarthroses and 2 hematomas treated with T was satisfactory.

In all cases, the peak of Factor VIII:C plasma level was obtained 60 min. post-infusion. The in-vivo recovery was 99 % of expected with NT and 95,5 % with T. This difference was not significant.

Calculated on 39 pairs of plasma samples collected at corresponding intervals, in the 6 patients, the mean FVIII:C plasma level obtained with NT was 0,269 u/ml and 0,223 u/ml with T. The correlation between these paired values was 0.976 and T levels were 17.1 % inferior to NT levels.

When calculated on samples collected beyond 1 hour post-infusion, the average FVIII:C half-life was 9 hours for NT and 8 h for T. Such results were not significantly different.

In addition, Factor VIII recoveries and half-liwes were measured in two patients after the third infusion of the treated material. No change in either parameter was detected when compared to the first infusion of treated concentrate.

Paris, January 21, 1982 GRO-C d P. Allain п.Д.

#### PATIENTS

1 - GRO-A

2 – GRO-A

3 – GRO-A

4 – GRO-A

5 – GRO-A

GRO-A

6 -

29,5 kgHematocrit36-37 %Bleeding site : right ankleDoses27 - 25 u/kg

27 kg Hematocrit 41-39 % Bleeding site : left elbow Doses 29 - 27 u/kg

27,9 kg Hematocrit 37-35 % Bleeding site : NT right knee, T. left deltoid Doses 28 - 26 u/kg

23,9 kg Hematocrit 36-37 % Bleeding site : NT right knee, T left deltoid Doses 28 - 26 u/kg

28,5 kg Hematocrit 36-34 % Bleeding site : NT chest hematoma, T right elbow Doses 27.8 - 35.6 u/kg

25,7 kg Hematocrit 37-38 % Bleeding site : NT soft tissue, T. right thigh Doses 30.8 - 28.5 u/kg

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IN VIVO	RECOVERIES	a	=	Not treated
		b	=	Treated.
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Factor VIII:C (u)

			فيهم بمسياب المتعار المتعار المتعال المتعاد المستاح المتعاد المتعاد المتعاد المتعاد المتعاد المتعاد ا			ويبيه ومحمل البراغات والمتحر والمحرب والمحرب والمحرب والمحرب والمحرب والمحرب والمحرب والمحرب والمحرب			
<u>,</u>	Patient	Before	15 min	30'	60'	4 h	12 h	24 h	48 h
C	la	- 0.01	0.19	0.265	0.51	0.345	0.195	0.047	0.026
	ď	- 0.01	0.155	0.29	0.45	0.255	0.135	0.035	0.011
$\sim$	2 a	- 0.01	0.21	0.30		0.43	0.25	0.046	0.02
	b c	- 0.01 - 0.01	0.175	0.255 0.32	0.46 0.535	0.25 0.35	0.145 0.185	0.03	- 0.01 0.04
$igcap_{i}$	3 a	- 0.01	0.195	0.29	0.57	0.46	0.31	0.102	0.042
	( b	- 0.01	0.15	0.27	0.53	0.37	0.225	0.08	0.03
C	4 a	- 0.01	0.27	,0.355	0.665	0.57	0.305	0.102	0.056
-	b c	- 0.01 - 0.01	0.225	0.315 0.27	0.60 0.615	0.39 0.34	0.25 0.215	0.08 0.096	0.035 . 0.047
Q	Ca	- 0.01		0.32	0.55	0.37	0.225	0.067	0.037
	b	- 0.01		0.28	0.515	0.31	0.19	0.046	
Ç,	6 a	- 0.01	0.215	0.30	0.575	0.385	0.26	0.063	0.033
	b	- 0.01	0.21	0.28	0.51	0.30	0.21	0.06	0.025
	ومتوانية والمتجاهدة وتحريب المتحادين المتحر المتحدين								

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STUDY PROTOCOL AND DATA REPORT HYLAND - TRAVENOL HE	OFIL L	OT.Nos.		
				-
Patient initials $GRO-A$ Birthdate $GRO-C$ $G_{I}$	W	eight L	,2,5,.7	
Hemophilia A diagnosed 1	us 📖			1
mo d. yr Last previous AHF <u>19 .92, 81</u> , 11.21.81product used	Blce	ding N	vot blee CNT	eding S
mo d. yr Last blood transfusion <u>اعبر کارکار</u>	cryo p	pt. Co	mercia	al cor
mo d. yr CLINICAL AND LABORATORY DATA				
	Lot nu	iber :		
1	T 4'	USION M	T JABER	T
•	1	2	3	1. 4
Date of Bleed	10-1-21	1.7.82		ļ
Time of onset of Bleed				ļ
Time of starting AHF infusion after Bleed				
Time of finishing AHF infusion	<u> </u>			
Fibringen pre-infusion r les / ums	1125/175	210/205		
FSP pre-infusion				┼
Factor VIII antigen pre-infusion VIII: CAg				
Concentrate injected (UFVIII) dosace U/kg				1
Factor VIII activity in vivo U/ml				1
pre-infusion	-0.01	- 0.01		
post-infusion 15'	0.215			1
30'	0.30			1
<u> </u>	0.575	0.51		<u> </u>
<u> </u>	0.26	0.30		
. 24 hrs	+	0.06		1
	1 0.033	0.025		
* <u>Plasma volume (ml)</u> = <u>30 x kg body wt. x (100 - hematocrit</u> ) 100	1295	1274		-
Amt.of FVIII : c injected = value given by 1 or 2 stage assay x injected volume	790	730		
Theroretical peak of FVIII:c = amt.of FVIII: c injected plasma volume	0.61	0.57		
Percent in vivo recovery = actual FVIII: c x 100 theoretical FVIII :c	94	83		
* Ref.Allain, J.P., Verroust, F.and Soulier, J.P. Vox Sanguinis, 38:68-80, (1980)				
<pre>%% 5xl.Oml serum pre infusion for Prof.Masson, store at 20°C %%% 5xl.Oml serum post-4h.infusion +</pre>	<u>**</u> 1 wk.f	er Mas	son	
Date :. $\frac{1.13.\xi L}{M}$			Albin stigato	)r

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Travenol 1 and 2 are to be returned to R Travenol International Services, Inc.	Investigator	other	urticaria	resp.distress	back pain	nausea	Adverse effects	end of infusion		Blood Pressure before	Observations during infu- sion	Other treatment		Circumferential measurement if relevant, after 24 hrs.	Circumferential measurement if relevant, before treat.	Bleeding -another site after 24 hours	24hrs.after	Pain <u>Before</u>	Bleeding Site		FSP	Fibrinogen	Hematocrit %		
are to be retu rmational serv ©	or .						yes		B	6	Systolic	imesuly sarim	ON	· r.				yes	Soft h				24/1/1	Pre- 30 60 inf min min	Infusion nº J
(A)		0	3	4	5	€ .	ou .		ч	വ	Systolic <sup> </sup> Diastolic	Jatim		CIN	сm	<u>k</u>	R	no	rissue				11/11/1	24 48 11r 11r.	on n°I
Sikart, M.D. Mulical Director Baroje, Do chamasice de La Ibilas, 1050 Brussels, O							yes.		10	11	Systolic Diastolic	im ohilization	۵۷	29154.5133	29/54.			yes	right Hrigh				2012	re- 30 60	Infusion nº2
Lu Hulps, 102	CNT(		6 8	8	ъ	~	011		S	2	Diastolic	Jata	0	- 139 cm	54.5/39 cm	8	8	110	y Br	<u>C1,11</u>				4.8 hr	11 11 2
8	21						yes				Systolic							yes		CLINICAL ASSES	$\square$	Ž		're- 30 60	Infusio
Q (	1						no				Diastolic			Cm	cm.			no		SSUENT				n hr hr i	
							yes				Systolic [							yes						Pre- 30 60	Infusion n <sup>v</sup> 4
)	Date 1 m.						no				Diastolic			ст	cm			Du					<u>  </u>	24 48 hr	n°4
Q	15 SL						yes				Systolic I	-											1111	rc 30 60	Infusion
୍ (							00	•			Diastolic			ст	ĊĦ			no						24 48	n "5
<b>-</b> • •	. Z	98	ъą													•							•	۴.	

...!! ·: 45 STUDY PROTOCOL AND DATA REPORT HYLAND - TRAVENOL HEMOFIL LOT. 200401 AH IL 5 Weight ...2.8.5 GRO-C 71 **GRO-A** Patient initials Birthdate Patient status <u>b</u> Bleeding Not bleeding mo d. yr ( 11, 15. 81, Product used \_\_\_\_\_\_\_ cryo ppt. Last previous AHF Commercial conc.br. m d. yr 11, 15,81 Last transfusion •{ mod. yr

#### CLINICAL AND LABORATORY DATA

	I IN:	USION N	UNEER	
	1	2	3	4
Date of Bleed	12.2.11	112-10.81	1-11-82	1-23-82
Time of onset of Bleed	<u> </u>			
Time of starting AHF infusion after Bleed				
Time of finishing AHF infusion	+15'	+12,		
Platelets pre-infusion	171	165		
Fibrinogen pre-infusion	-	-		
FSP pre-infusion				
Factor VIII antigen pre-infusion				
Concentrate injected (UFVIII) dosage U/kg				
Factor VIII activity in vivo U/ml				
pre-infusion	0.011	0.01		
15'	-	-		
30'	0.32	0.18		
60'	0.55	0.515		
4 hrs.	0.57	0.71		
12 hrs.	0.225	0.19		
24 hrs.	0.067	0.046		
48 hrs.	10.057			
$\frac{\text{* Plasma volume (ml)}}{= 30 \times \text{kg body wt. x (100 - hematocrit)}}$	1436	14 89		
Amt.of FVIII : c injected = value given by 1 or 2 stage assay x injected volume	730	730		
Theroretical peak of FVIII:c = amt.of FVIII: c injected/plasma volume Percent in vivo recovery	22	49		
<pre>= actual FVIII: c x 100 theoretical FVIII :c * Ref.Allain, J.P., Verroust, F.and Soulier, J.P. Vox Sanguinis, 38:68-80, (1980)</pre>	୲୰ଡ଼	105		

1,5,82 Date : M D

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	Infus Pre- 30	n°1 24 48	30 30	<mark>n°2</mark> 24 48	1 30	n°3 24	• • • • • • • • • • • • • • • • • • • •	م°4 24	0   30	F
7	Luf min m	1	inf. min.Min.	hr hr	inf min m	min hr hr	uin	min hr hr	inf min min	n hr ar
Fibrinogen	1		1.							
FSP					$\square$					
				CI.IN	CLINICAL ASSESSMENT	TN:INSS:				
Bleeding Site	Right Rectoral	letral	Right Man	Abow	USL SN	r Ineanu.	right elbour	bour		
Pain Before	yes yes	8 2	yes A	02	ves	ou	yes	or	yes	ou
24hrs.after		ه		۶		<u>ک</u>				[
Bleeding -another site after 24 hours		ନ		R						
Circumferential measurement if relevant, before treat.	u	E		ш		ш С	-	E	·	EU
Circumferential measurement if relevant, after 24 hrs.	IJ	Ę		EO		ED		шIJ		сп
Other drugs used										
Other treatment			immetri	immetri way tring						
Observations during infu- sion	Systolic	Systolic Diastolic	Systolic	Systolic Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
re	11	و	10.5	S						
After 5 <sup>1</sup>	=	S	11	S						
end of infusion		-								
Adverse effects	yes	ou	yes	ou	ycs	ou	ycs	ou''	ycs	ou
cullis nausea		عاد		٩٩		8		R		
back pain		d		۶		۶		9		
resp.distress		R		۶.		s.		8		
urticaria		ء م		8-2				84		
other						)-  		27		
29 Allain Investigator	or			C N 7 Hospital	Y L			Date   m.	L L .	4
			- 11	the factor						6
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	TRAVENOL	47
· · ·	SIUDY PROTOCOL AND DATA REPORT HYLAND -	۲۵.۵۹.۰۱ ۲۹ ۱۱۵ ۲۵.۵۹.۰۱ ۲۹ ۱۱۵ ۲۳۸۷ENDL HENDFIL LOT.
0	Patient initials <b>GRO-A</b> Birthdate	GRO-C, TU, Weight 12.3.8
(	Hemophilia A diagnosed <u>11174</u> mo d. yr Last previous AHF <u>9,24,71</u>	Patient status <u>p</u> Bleeding Not bleeding Product used <u>p</u>
ି	mod.yrLast transfusionmod.yrmod.yr	cryo ppt. Commercial conc.bra

#### CLINICAL AND LABORATORY DATA

	I DE	USION N	UNBER	-
	1	2	3	4
Date of Bleed	10.5.81	111-12-81	13.8.51	1.15.8
Time of onset of Bleed	<u> </u>			
Time of starting AHF infusion after Bleed				
Time of finishing AHF infusion	+ 20'	+ 15'		
Platelets pre-infusion X 101	1171	161	1	
Fibringen pre-infusion	-	-		
ISP pre-infusion	1			
Factor VIII anticen pre-infusion				
Concentrate injected (UFVIII) dosage U/kg	33.2	30.7		30.7
Factor VIII activity in vivo U/ml				
pre-infusion	- 0.01	- 0.01	•	-0.01
、 15'	0.27	0.225		
30'	0.355	0.315	!	0.27
60'	0.665		1	0.615
4 hrs.		0.39		0.34
12 hrs.	0.305	0.25	· ·	0.215
24 hrs.	0.102		İ	0.09
48 hrs.		0.035		0.04
* Plasma volume (ml)				
= $30 \times \text{kg}$ body wt. x (100 - hematocrit)	1221	1202		1161
100	1001	1000	1	
Amt.of FVIII : c injected				
= value given by 1 or 2 stage assay x injected volume	430	730		730
Theroretical peak of FVIII:c				62.9
= amt.of FVIII: c injected/plasma volume	64.7	60.7		60.2
Percent in vivo recovery				
= actual FVIII: c x 100 theoretical FVIII :c				
# Pof Alloin T.D. Verrough F. and Couling T.D.	102	98		98
* Ref.Allain, J.P., Verroust, F.and Soulier, J.P.		-		
Vox Sanguinis, 38:66-80, (1980)				

Date : 1.5.92 M D Yr

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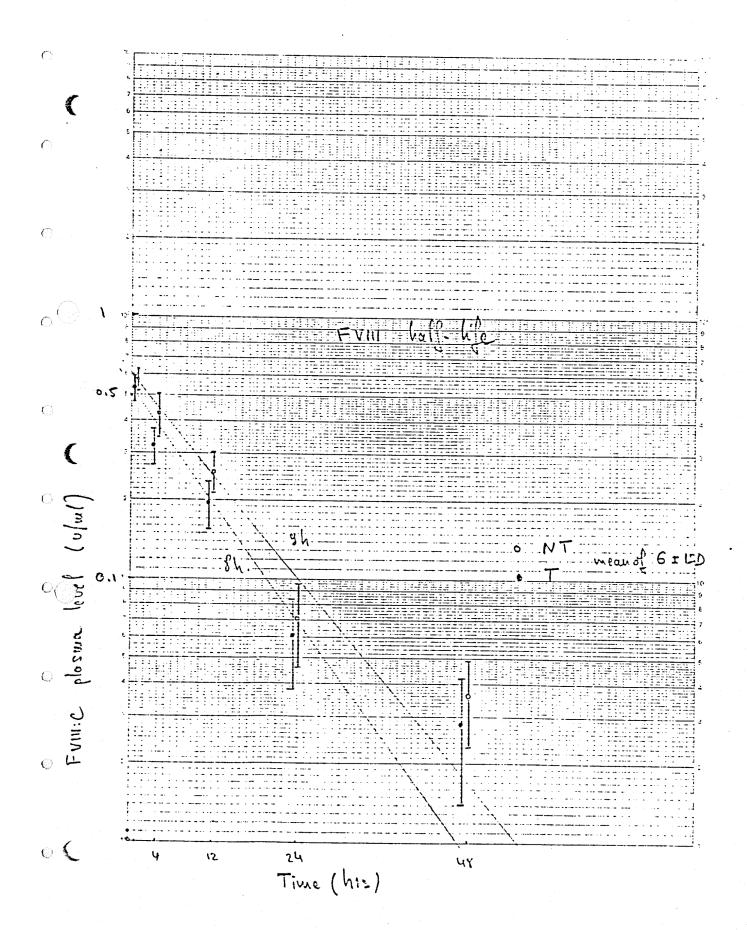
	90	24	30	24 48	Pre- 30 6	30 60 24 48	Pred 30	60 24 4		60 24 46
Hcmatocrit 7 Fibrinogen	inf mir m 3.6	min IIr IIr.	inf. min M		nin	u lir	inf min		inf min	
FSP										
			÷	<u>CI.I</u>	CLINICAL ASSESSMENT	ESSMENT				, <u>, , , , , , , , , , , , , , , , , , </u>
Bleeding Site	Right Bulitia	betterid	Night	Luce	Right	el baur	Jugger	elbeur		
Pain Before	Yes Yes	2 []	yes		ycs	2 []	, yes	1	Acs	ou
24hrs.after		Z		٩						
Bleeding -another site after 24 hours				8						
Circumferential measurement if relevant, before treat.	ц	E	26	E		EO				]  [
Circumferential measurement if relevant, after 24 hrs.	υ.	Ę	22			E		Ē		Ę
Other drugs used	1									
Other treatment										
Observations during infu- sion	Systolic	Systolic Diastolic	Systolic	Diastolic	Systulic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Blood Pressure before	10.5	N	n	ي						
After 51	1	S	5.01	2						
			•			-				
Adverse effects	yes	ou	yes	ou	ycs	ou	ycs	ou	yes	ou
Chills		7 8		79		,		~		
back pain		٩				25		2		
resp.distress		. Q		.2		2 2		2		
urticaria		æ		\$				ر ه		
itching		٦		\$		٩		- 2		
<u>AY H Ualu</u> Investigator	יי א			C W 1 Ilospital	S-I-I	1		Date /	5.71	-
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STUDY PROTOCOL AND DATA REPORT HYLAD - TRAVENOL HENDFIL LOT.

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Patient initials GRO-A GRO-C 71, по а. уг Birthdate Patient status Bleeding Not bleeding mod. yr Last previous AHF . 10.1.71. Product used b. Commercial conc.bra mod. yr Last transfusion 10,1,81, .( mod. yr

## CLINICAL AND LABORATORY DATA

		USION N	U.IEER	
Date of Bleed	1	2	3	4
	10.13.21	10.23.81	112-27-81	
Time of onset of Bleed				
Time of starting AHF infusion after Bleed	1	1		
Time of finishing AFF infusion	+ 20'	+15		
Platelets pre-infusion	261	280		
Fibrinogen pre-infusion	-	-	·	
FSP pre-infusion Factor VIII antigen pre-infusion				
· Concentrate injected (UFVIII) dosage U/kg	1281			
	28.3	26		
Factor VIII activity in vivo U/ml				
pre-infusion	- 0.01	- 0.01		
15'	0.195	0.15		
<u>`30'</u> 60'		0.27 1		
4 hrs.	0.57	0.531		
12 hrs.	0.46	0.37		
24 hrs.	0.11	0.1251	1	
48 hrs.	0.102	0.07 1		·
	0.042	0.02		
$\frac{\text{Plasma volume (ml)}}{= \frac{100 \text{ x kg body wt. x (100 - hematocrit)}}{100}}$	1406	1451		
Amt.of FVIII : c injected = value given by 1 or 2 stage assay x injected	750	730		
volume <u>Theroretical peak of FVIII:c</u> = amt.of FVIII: c injected/plasma volume <u>Percent in vivo recovery</u>	26	20.7		
<pre>= actual FVIII: c x 100 theoretical FVIII :c * Ref.Allain, J.P., Verroust, F.and Sculier, J.P. Vox Sanzuinis, 38:68-80, (1980)</pre>	102	105		

Date : 1, 5, 92M D Yr

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C	30	8  Pre 30 )	24 48	Pre- 30 6	24 48	Pre- 30 60	60 24 4	hred 30 60	0 24 43
llematocrit Z Fibrinogen	inf min min llr Hr 57 -	inf. min 35		ui li	hr hr	min		min	hr.
FSP				$\square$					
			CI.IN	CLINICAL ASSESSMENT	SSHENT				
Bleeding Site	Right Kuce	lyt Deltoid	(toid	left foreanu	- and				
Pain Before	, the no the second sec	yes V	01	ycs	ou	yes	ou	yes	02
24hrs.after			2						
Bleeding -another site after 24 hours			R						
Circumferential measurement if relevant, before treat.	t 28.5 cm	E	E		E		E		80
Circumferential measurement if relevant, after 24 hrs.	t 28.5 cm		E		EO		EC		E
Other drugs used									
Other treatment		inuolisatin	isatim						•
Observations during infu-	Systolic Diastolic	11	<u>ب</u> .	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Blood Pressure before	y 11	0	6						
	10.5 6	10	6						
end of infusion									
Adverse effects	yes no	yes	ou	ycs	ou	yes	ou	yes	ou
Chills	29		85		84				
back pain	5		29		28				
resp.distress	.9-		. 2		28				
urticaria	Å		8		2				
itching	8		8		٩			·	
				l				1	
Investigator	11		llospital	1			Date (	12 5	_
								,	

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Patient initials GRO	A Birthdate	GRO-C 70. Weigh	t <u>2,7</u>
Hemophilia A diagnosed	1 1 72	Patient status 🔔	4
	mod.yr	Bleeding	Not bleeding
Last previous AHF	19,10,81,	Product used	J
	mod.yr	cryo ppt.	Commercial conc.br
Last transfusion	19,10,11,	•	
	mod.yr		

#### CLINICAL AND LABORATORY DATA

· · · · · · · · · · · · · · · · · · ·	I INF	USION N	UNEER	
	1	2	3	4
Date of Bleed	9.28.81	10.19.81	111.16.71	12.3.91
Time of onset of Bleed				
Time of starting AHF infusion after Bleed				
Time of finishing AHF infusion	+12,	+ 10'		
Platelets pre-infusion ¥ 10-3	1250	257		
Fibrinogen pre-infusion	3.2	3		
FSP pre-infusion				
Factor VIII anticen pre-infusion				
Concentrate injected (UFVIII) dosage U/kg	29.2	27		27
Factor VIII activity in vivo U/ml				
pre-infusion	- 0.01	-0.01		-0.01
15'	10.21	0.175		
· 30'	0.295	0.255		0.32
60'	-	0.46		0.535
4 hrs.	0.43	0.15		0.35
12 hrs.	0.15	0.145		0.185
24 hrs.	0.046	0.03		0.061
48 hrs.	0.02	-0.01		0.04
$\frac{\text{Plasma volume (ml)}}{= \underbrace{\text{80 x kg body wt. x (100 - hematocrit)}}_{100}}$	1274	1517		1236
Amt.of FVIII : c injected = value given by 1 or 2 stage assay x injected volume	790	730		730
The foretical peak of FVIII:c = amt.of FVIII: c injected/plasma volume Percent in vivo recovery	<b>\$</b> 2	55.4		56.3
= actual FVIII: c x 100 theoretical FVIII :c	-	83		95
* Ref.Allain, J.P., Verroust, F.and Soulier, J.P. Vox Sanguinis, 38:68-80, (1980)				

Date : 1.5.72M D Yr

JP Allaiy Investigator  $\frac{C \cdot N \cdot T \cdot S}{Hospital}$ 

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STUDY PROTOCOL AND DATA REPORT HYLAND - TRAVENOL HEMOFIL LOT.

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Patient initials GRO-A	Birthdate	mod.yr	Weight	2.9.5	
Hemophilia A diagnosed	<b>└──-!</b>	Patient status	<u> </u>	<u>ــــــ</u>	
	mod.yr	В	leeding	Not bleed	ing
Last previous AHF	20.8.81	Product used	×	1	
	mod.yr	cry	o ppt.	Commercial	conc.br
Last transfusion	18, 8, 01				
	mod.yr				

## CLINICAL AND LABORATORY DATA

		USION N	UNBER	
	1	2	3	4
Date of Bleed	12-10-81	120.10-81	186-11-81	1-25-8
Time of onset of Bleed				
Time of starting AHF infusion after Bleed				
Time of finishing AHF infusion	+ 15 min	+ 1Swin		
Platelets pre-infusion x 103	275	283	1	
Fibrinogen pre-infusion	2.3	2.8		
FSP pre-infusion				
Factor VIII anticen pre-infusion			1	
Concentrate injected (UFVIII) dosage U/kg	26.9	24.9		
Factor VIII activity in vivo U/ml				
pre-infusion	- 0.01	- 0,01		
15'	0.19	0.155		
` 30'	0.265	0.29		
60'		0.45		
4 hrs.		0.255		
12 hrs.		0.135		
24 hrs.		0.035		
48 hrs.		0.011		
* <u>Plasma volume (ml)</u> = <u>30 x kg body wt. x (100 - hematocrit)</u> 100	1500	1476		
Amt.of FVIII : c injected = value given by 1 or 2 stage assay x injected volume	790	750		
The/oretical peak of FVIII:c = amt.of FVIII: c injected/plasma volume Percent in vivo recovery	52.7	49.5		
= actual FVIII: c x 100 theoretical FVIII :c	86.7	31		
* Ref.Allain, J.P., Verroust, F.and Soulier, J.P. Vox Sanguinis, 38:68-80, (1980)				

M D Yr Date :

J.Q. Allain Investigator

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Paris C.N.T.S. Hospital

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L1     cm     cm     cm       Systolic     Diastolic     Systolic     Diastolic     Systolic       Systolic     Diastolic     Systolic     Systolic     Systolic       Systolic     N     N     N     N       V     P     N     N     N       V     N     N     N     N       V     N     N     N     N       N     N     N     N     N       N     N     N     N     N       N     N     N     N     N       N     N     N     N     N       N     N     N     N     N       N     N     N     N     N	2lcmcmcmcmSystolicmcmcmcmSystolicDiastolicSystolicDiastolicSystolicSystolicSystolicDiastolicSystolicDiastolicSystolicSystolicSystolicSystolicDiastolicSystolicSystolicSystolicSystolicDiastolicSystolic	if relevant, before treat. 21.5				сщ	E C		E C
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Martin Constant

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(	Patient initialsGRO-ABirthdayHemophilia A diagnosed $1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1$	te GRO-C 71 Weight 12,7,9 Patient status 2 Bleeding Not bleeding Product used 2 cryo ppt. Commercial conc.br

# CLINICAL AND LABORATORY DATA

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Date of Bleed	-1	2	1 3	4
	10.13.2	1/ 10.25-31	112-27-81	2-22-
Time of onset of Bleed				1
Time of starting AHF infusion after Bleed		1	İ	
Time of finishing AFF infusion	+ 20'	+15		
Platelets pre-infusion	261	1 280		
Fibrinogen pre-infusion		-		
FSP pre-infusion		1		
Factor VIII antigen pre-infusion	1		· · · · · · · · · · · · · · · · · · ·	
Concentrate injected (UFVIII) dosage U/kg	28.3	26		
Factor VIII activity in vivo U/ml	1			
pre-infusion	- 0.01	- 0.01		
15'	0.195			
<u>30'</u>	0.19	0.27 !		
		0.531		
4 hrs. 12 hrs.	0.46	0.37		
24 hrs.		0.125		
48 hrs.	0.101	0.07 1		
	0.0421	0.021		
* $\frac{\text{Plasma volume (ml)}}{= 30 \text{ x kg body wt. x (100 - hematocrit)}}$ 100		1451		·
Amt.of FVIII : c injected = value given by 1 or 2 stage assay x injected volume	720	730		
= amt.of FVIII: c injected/plasma volume Percent in vivo recovery	56	20.3		
<pre>= actual FVIII: c x 100 theoretical FVIII :c * Ref.Allain, J.P., Verroust, F.and Soulier, J.P. Vox Sanzuinis, 38:68-80, (1980)</pre>	10.5	105		

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llematocrit Fibrinogen FSP	Bleeding	Pain	•	Blecdin after	Circumf if rel	Circumf if rel	Other d	Ocher t	Observa	Blood	<u></u>		אמא הי אמן אמן				-			

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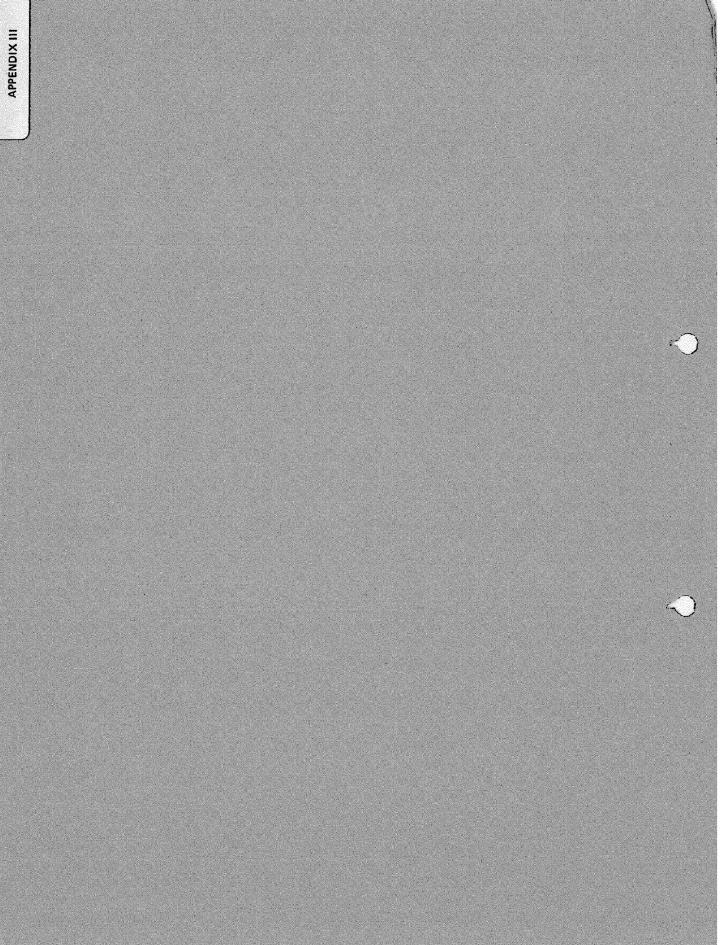
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	TRAVENOL			Page 1	
STUDY	PROTOCOL AND DATA REPORT HYLAND - TRAVENOL HEN	OFIL I	DT.Nos.		_
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	centrate injected (UFVIII) dosace U/kg			i i	 
	pre-infusion post-infusion 15'	.0.01	- 0.01	1	
	30' 60'	0.30	0.29		1
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* 1	48 hrs.	0.035	0.025		   •
	= <u>30 x kg body wt. x (100 - hematocrit)</u> 100 Wmt.of FVIII : c injected	1295	1274		
	= value given by 1 or 2 stage assay x injected volume	790	730		· · · ·
	heroretical peak of FVIII:c = amt.of FVIII: c injected plasma volume Percent in vivo recovery	0.61	0.57		
	= actual FVIII: c x 100 theoretical FVIII :c ef.Allain, J.P., Verroust, F.and Soulier, J.P.	94	83		
	ox Sanguinis, 38:68-80, (1980)	:*:	* <b>*</b>		
	Prof.Masson, store at 20°C *** 5x1.0ml serum post-4h.infusion + 1	l wk.f	or Mas	son	
	Date :. $\frac{1.13.5L}{M D Yr}$ .		Inve	Huin stigator	
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## APPENDIX III

## ASSAY OF CIRCULATING IMMUNE COMPLEXES IN

## HAEMOPHILIAC PATIENTS (PROF. MASSON, BRUSSELS, BELGIUM

The assay of circulating immune complexes in hemophilic patients

#### Samples

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Two groups of serum samples were analyzed separately. The first one comprised 12 samples from 3 patients and, the second, 11 samples from 3 other patients.

## Assay

The immune complex levels were determined by two tests based on inhibition of latex agglutination, using either rheumatoid factor (RF) or the so-called murine agglutinator (MAG) as agglutinating agents of the IgG-coated particles. The agglutination was measured in the PACIA system (Particle Counting ImmunoAssay) as described by Cambiaso et al. (J. Immunol. Methods, <u>23</u>: 29, 1978 and <u>26</u>: 3, 1979). The instrument is counting the residual non agglutinated particles of which the number is expressed in peak heights (see enclosed copies of the recorder sheet).

## Results

The results (Table 1) are given in equivalents of heat-aggregated IgG (see standard curves on recorder sheet). The above normal limit established on healthy blood donors is  $35 \ \mu g/ml$  for RF and  $350 \ \mu g/ml$  for MAG. As shown in Fig. 1 the results tended to be higher in the hemophilic patients than in blood donors (P < 0.001 for RF and MAG) but only two patients, de S.JP and BR had significant and constant abnormally high values (Table 1). The levels of immune complexes were slightly higher in the samples collected from some patients after repeated perfusion of treated Factor VIII (Table 1). However, the differences were not statistically significant in the Kruskal-Wallis rank test. The increase of immune complexes detectable by both RF and MAG tests was observed only in two patients FA and BR. The lack of correlation between the RF and MAG results (Fig. 2) can be explained by the differences of specificity of the two agglutinators regarding the size of the complexes and their antibody content.

## Conclusion

We confirm the tendency of hemophilic patients to have higher levels of circulating immune complexes. No significant increase was noted after three perfusions of the new preparation of Factor VIII.

> March 1182 Prof. T. C. MASSON

GRO-C

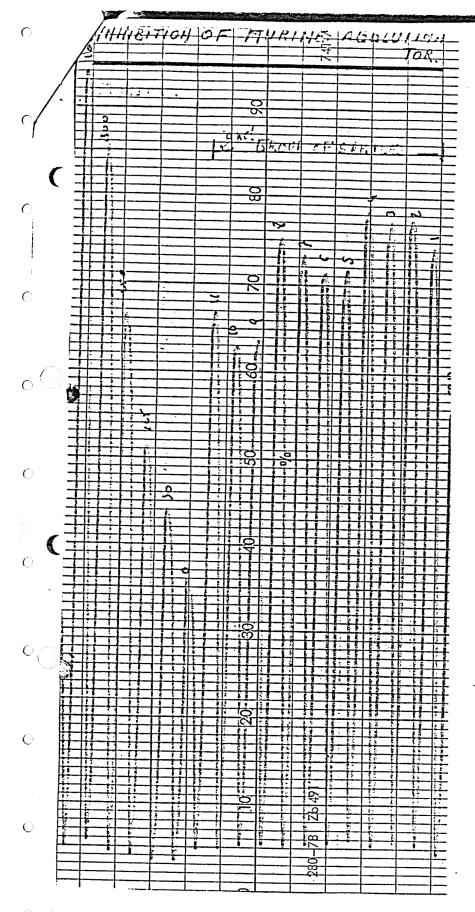
$\geq$	Patients	Tests		Time of s	ampling	
	:		Before untreated FVIII	10-15 days after untreated FVIII	10-15 days after 1st treated FVIII	
1 	GRO-A	RF MAG	(5) Sept 28,1981 25 340	6 Oct 12, 1981 22 340	<pre>⑦ Oct 29, 1981 24 340</pre>	8 Dec 22, 1981 27 370
	GRO-A	RF MAG	<pre>③ Oct 5,1981 25 275</pre>	(10) Oct 17, 1981 27 325	(1) Nov 23, 1981 25 290	<ul><li>(2) Jan 29, 1982</li><li>30</li><li>280</li></ul>
⊖ <sub>[</sub>	GRO-A	RF MAG	<ol> <li>Oct 12,1981</li> <li>38</li> <li>325</li> </ol>	2 Oct 20, 1981 38 350	3 Oct 30, 1981 37 310	<ul> <li>4 Feb 2, 1982</li> <li>45</li> <li>270</li> </ul>
	GRO-A	RF MAG	(1) Oct 13, 1981 42 315	(2) Oct 23,1981 44 360	3 Nov 1, 1981 41 360	<ul> <li>4 March 4,1982</li> <li>47</li> <li>375</li> </ul>
	GRO-A	RF	5 Oct ?, 1981 32 275	6 Oct 12,1981 30 275	<ul> <li>Jan 26,1981</li> <li>30</li> <li>300</li> </ul>	<ul> <li>8 Feb 25, 1982</li> <li>32</li> <li>315</li> </ul>
	GRO-A	RF MAG	9 Dec 2, 1981 26 190	<ol> <li>Dec 10, 1981</li> <li>26</li> <li>180</li> </ol>		<ol> <li>Feb 15, 1982</li> <li>26</li> <li>220</li> </ol>
M R	RF = inhibit IAG = inhibit esults are g	ion of ion of iven i	es on the recorder rheumatoid factor murine agglutinat n equivalents of h for RF = 35 μg/ml for MAG = 350 μg/m	or eat-aggregated IgG ٦	(µg/ml)	
C	ithin-assay	precis	ion for RF : CV = for MAG : CV =	3.4 %		

Table 1. Levels of circulating immune complexes

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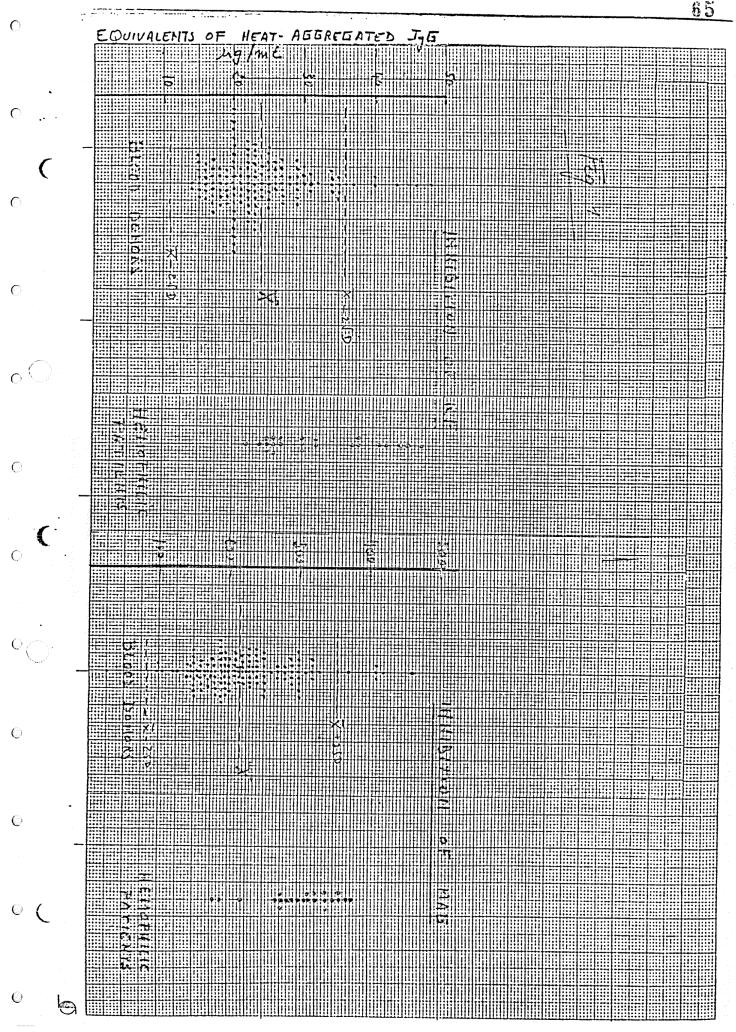
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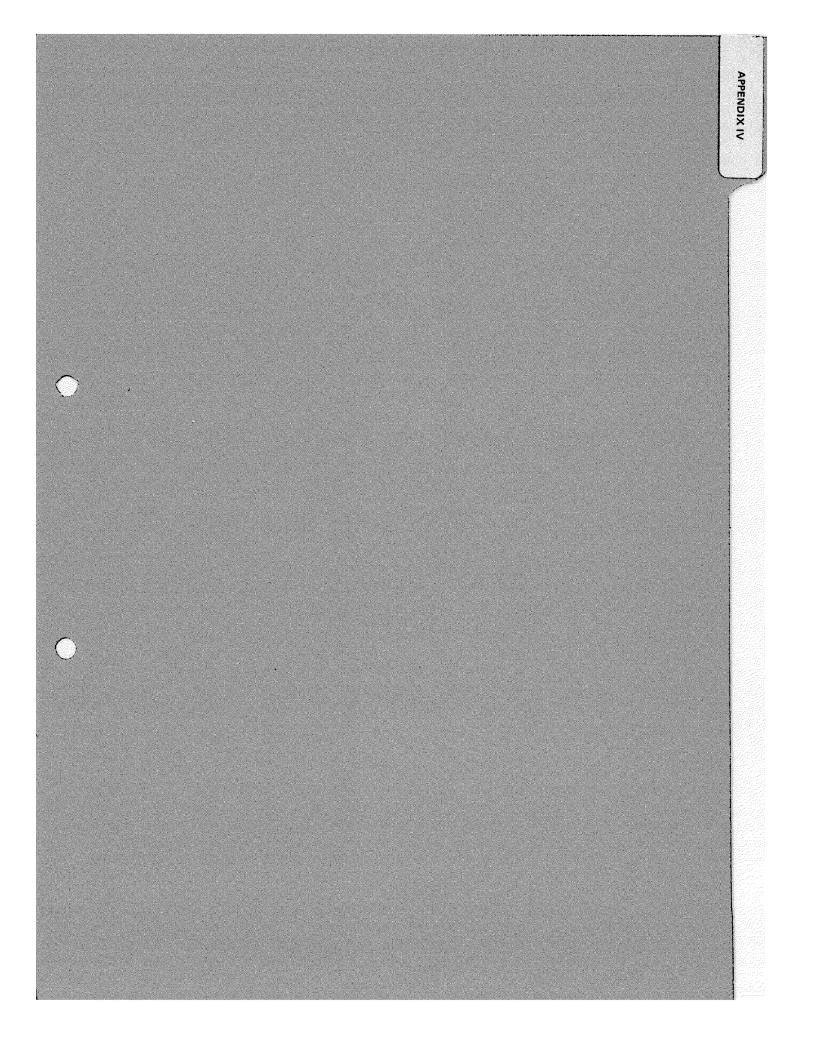
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### APPENDIX IV

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### AN ATTEMPT TO REDUCE THE RISK OF HEPATITIS

WITH HEAT TREATED FACTOR VIII CONCENTRATE -

INTERIM REPORT

(DR. COLOMBO AND PROF. MANNUCCI, MILAN, ITALY)

### AN ATTEMPT TO REDUCE THE RISK OF HEPATITIS WITH HEATED FACTOR VIII CONCENTRATE INTERIM REPORT

Presented by : M. COLOMBO - P.M. MANNUCCI

2nd International Workshop on Prevention in Hemophilia, Paris, February, 23-24, 1984

This is a report of the preliminary results of an ongoing multicentre clinical study of the use of a heat-treated F.VIII concentrate, Hemofil-T. The main objective of this study was to assess the attack rate of hepatitis in hemophilia A patients during administration of Hemofil-T. Additional questions were the type and severity of the hepatitis and its relationship to lots and doses of F.VIII concentrate (Fig. 1).

( )

Centres from 5 countries took part in this study (Fig 2). After 1 year enrolment (Dec. 82 - Dec. 83), patients were to be prospectively followed up for 12 months. Patients included in the study were hemophilia A patients of any age who had never been exposed to blood or any blood products (so-called virgin patients), with normal transaminase levels and no markers of hepatitis B infection except for those vaccinated against hepatitis B. Both patients on prophylaxis or on on-demand treatment, were included (Fig 3). The events monitored were post-transfusion hepatitis B, hepatitis A, cytomegalovirus, hepatitis viruses, namely hepatitis B, hepatitis A, cytomegalovirus, herpes and Epstein-Barr virus. PTH was defined according to internationally accepted criteria, i.e. as a rise in ALT values to more than 2.5 times the upper limit of the normal range on at least 2 consecutive occasions, 7 to 21 days apart, between 14 and 180 days after transfusion.

NANB hepatitis was diagnosed by standardised exclusion criteria. Questions to the patients about drugs and alcohol assumption were relevant for this diagnosis (Fig 4). Patients were to be followed up for a maximum period of one year, with serial clinical and laboratory assessments (Fig. 5). From December 82 to December 83, 34 patients were enrolled into the study. However, 12 had to be excluded from the analysis because they did not meet the selection criteria listed previously. The majority of them were non-virgin. Therefore, 22 patients are now being prospectively evaluated. So far, 14 patients have been followed for enough time (at least 3 months median 6 months) to provide preliminary data about the safety and efficacy of Hemofil-T administration (Fig. 6). Of these 14 patients, 9 developed NANB PTH, 1 had laboratory signs of CMV hepatitis and 4 were still hepatitis free after 5 to 13 months of follow-up.

Interestingly, none of the patients developed serum markers for HBV infection (Fig. 7). The incubation period for NANB PTH ranged from 4 to 12 weeks (median 6). However, this information refers only to the 6 patients who received the treatment in the very first days of enrolment.

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PTH was mild to moderate in all but one case, who developed jaundice. In fact, the median ALT peak was 8 times greater than normal; biliburin never exceeded 1.8 mg/ml in the 9 anicteric cases (Fig. 8). Figure 9 summarises the follow-up of all patients given Hemofil-T. Hepatitis is represented by the solid bars. An interesting finding was the lack of any relationship between frequency of treatment and PTH.

The case of CMV infection is shown as a broken bar. This patient was a three month old baby with transient, mild liver damage associated with a rise in anti-CMV IgM antibodies from 1:8 to 1:32. However, since the same lot of Hemofil-T was infused into another 6 patients without transmitting CMV infection, we believe this case of CMV hepatitis was not related to the treatment. Intrafamilial contacts were likely to be responsible for this case of CMV hepatitis (Fig. 10).

Among the cases with NANB hepatitis, patient No. 1 from Dr. Carnelli had a monophasic pattern of ALT abnormalities. ALT was moderately elevated and returned to normal within 12 weeks (Fig. 11). Another patient from Milan had a biphasic pattern of ALT abnormalities (Fig. 12): the first peak occurring 12 weeks after the onset of the study, the second peak 19 weeks later. Since the majority of the infusions overlapped with the incubation periods for NANB hepatitis, it is unclear whether the biphasic

pattern of ALT elevation is due to two distinct episodes of hepatitis or to reactivation cycles of the same infective agent.

Patients received a median total of 3,000 units of Hemofil-T, having been exposed to therapy a median of 5.5 times (Fig. 13). So far, we have found no relationship between PTH attacks and dosage of F.VIII concentrate (Fig. 14). The same was true for lots of Hemofil-T and PTH. However, it must be emphasised that only three lots of Hemofil-T have been assessed so far (Fig. 15).

In summary, 64% of the patients treated with Hemofil-T developed PTH. Hepatitis was invariably of the NANB type, anicteric in all but one instance, and of moderate degree (Fig. 16). The lack of a control population makes it impossible for us to compare the attack rate of Hemofil-T-related PTH with that related to administration of regular factor VIII concentrates. However, reports in the literature indicate that NANB hepatitis in patients who were first exposed to the regular concentrates may be more frequent and severe than that reported here. Obviously, it is too early to define the risk of chronicity in patients with Hemofil-T-related hepatitis.

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The other facet of the same investigation is to know whether exposure of Hemofil-T will vaccinate the patients against a more severe form of PTH. None of the patients in our study developed serum markers for HBV. This might reflect more accurate selection of the plasma donors, but further follow-up of these patients is required to rule out the occurrence of delayed HBV infection with prolonged incubation.

Finally, all the investigators reported that the efficacy and tolerance of this product were equal to those recorded for the regular concentrates (Fig. 17).

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### Addendum to the Interim Report

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The status of the study as at 26th July, 1874 is as follows:

20 virgin patients have been followed for at least 3 months the majority for more than 6 months although some will not complete a full year of follow-up. We now have 174 patientmonths of clinical and laboratory data for assessment.

None of the 20 virgin patients now receives prophylaxis; 15 are receiving on-demand therapy while the other 5 received short treatments for surgery or dentistry.

Of these 20 patients, 13 have shown elevated ALT levels (>100 IU/1) but only 11 meet Dr. Colombo's criteria for posttransfusion hepatitis, giving an incidence of non-A, non-B hepatitis of 55%. This compares favourably with the 64% calculated from the last assessment in February. The other two cases of elevated transaminases were due to CMV infection and an isolated peak not interpreted as hepatitis.

It should be noted that no clinical signs or symptoms of hepatitis have been seen with the exception of one patient who developed post-surgical jaundice. No case of seroconversion for hepatitis B has occurred although only 6 of the 20 patients were vaccinated against hepatitis B.

### **EUROPEAN CLINICALS** OBJECTIVES HEMOFIL T

### OVERALL : ASSESS THE ATTACK RATE **OF HEPATITIS**

SUBSIDIARY QUESTIONS :

- Severity
- Chronicity
- Type of Hepatitis
  - -ot relationship
- **Dose relationship** 
  - - Tolerance
      - - Efficacy

FIGURE 1. 72

### **HEMOFIL T CLINICALS** DESIGN

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### **MULTICENTER STUDY**

□ Italy

Germany 

□ France

□ Luxembourg

Carnelli

- Mannucci
- Schimpf

■ Klose

- Savidge
- Aronstam
- Pommereuil
- Gazengel
- Larrieu
- Dicato

Follow-up 12 months **PROSPECTIVE : NO CONTROL ENROLLMENT:** 

**December 82 - December 83** 

FIGURE ~ ~1 CL2

## INCLUSION CRITERIA

- Hemophilia A patients
- Normal liver enzymes
- □ Virgin (×)
- Vaccinated / Non vaccinated against Hepatitis B
- □ Any age
- Any bleed, surgery, prophylaxis

retrospectively to be scientifically hard to interpret. (\*)Non virgin also enrolled but data showed

### DIAGNOSIS OF NANB HEPATITIS **BY EXCLUSION OF**

KNOWN HEPATOTOXIC DRUGS AND ALCOHOL HEPATOTROPIC VIRUSES

- Hepatitis B
- Hepatitis A
- Epstein Barr
- Cytomegalo
- Herpes

## TIMING OF LABORATORY AND CLINICAL ASSESSMENT

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- Ist assessment
- 1st infusion of Hemofil
  - Every two weeks
- Every three weeks

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== Monthly

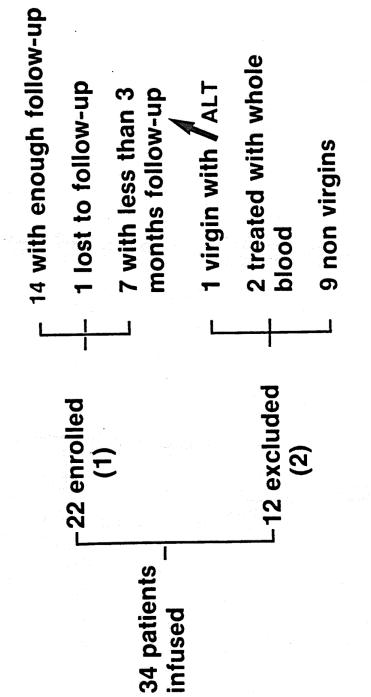
7-12 MONTHS

2-6 MONTHS

**1ST MONTH** 

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(1) Three lots infused(2) Four lots infused

FIGURE 6.

RESULTS

- 9 NANB Hepatitis (64%) - 1 CMV infection (7%) 14 assessable patients

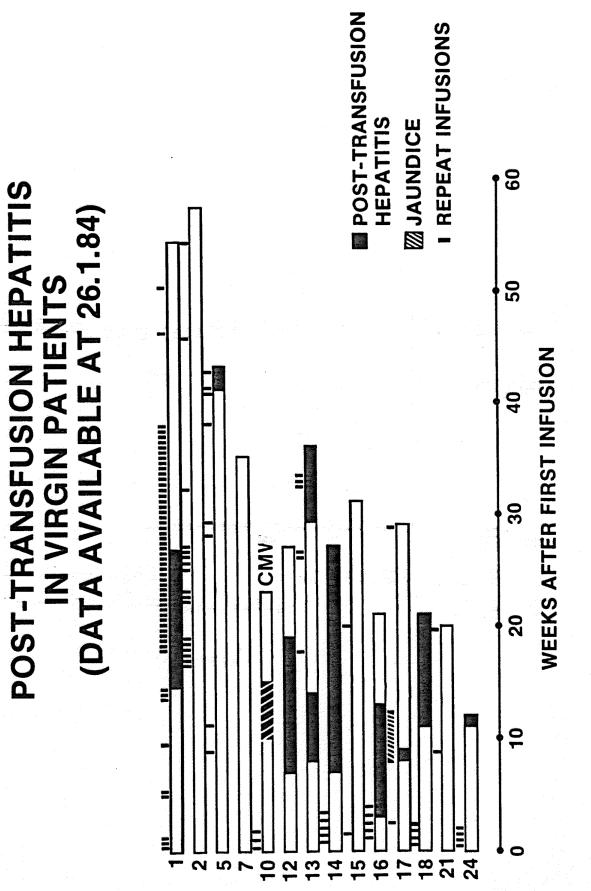
- 4 no Hepatitis (29%)

CLINICAL AND LABORATORY FEATURES OF NANB HEPATITIS

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0 –	Range       Median         0.2 - 58       2.5         4 - 12(*)       6         4 - 91       8         0.44 - 10.70       1.11	
NUMBER OF PATIENTS CLINICAL SYMPTOMS AT ONSET OF ALT	AGE (YEARS) INCUBATION (WEEKS)(*) ALT LEVELS (x NORMAL) BILIRUBIN (PEAK)(mg/dl)	

(\*) Only 6 patients are assessable



# HEMOFIL T STUDY POST-TRANSFUSION HEPATITIS

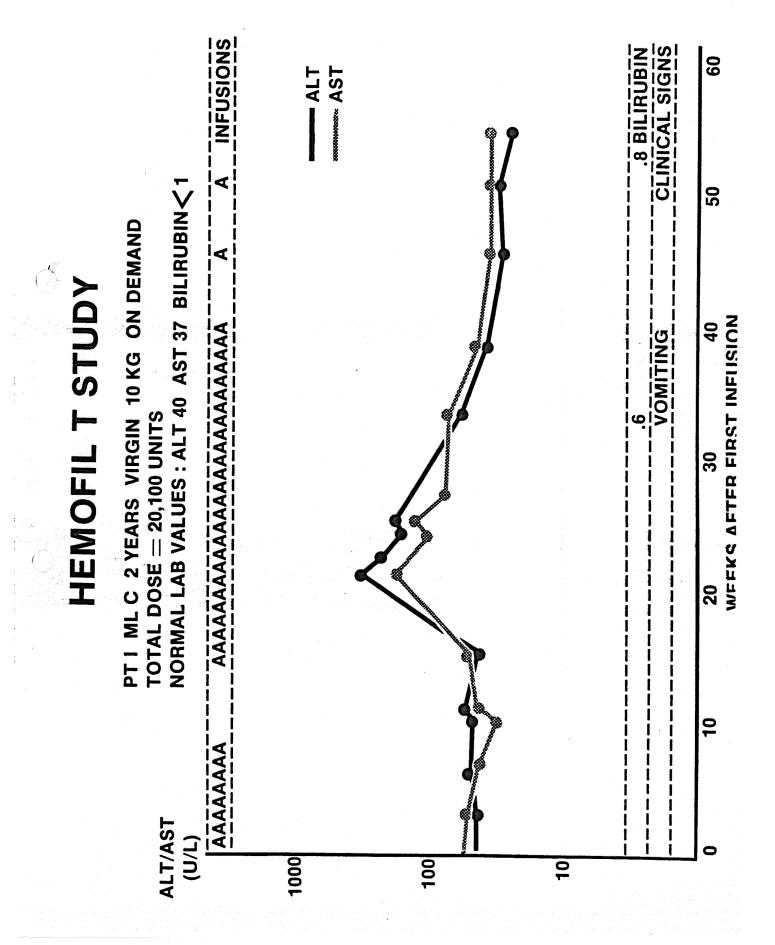
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## THE C.M.V. CASE

□ Six other patients receiving same lot did not show seroconversion

□ Low titers



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FIGURE 11. 82

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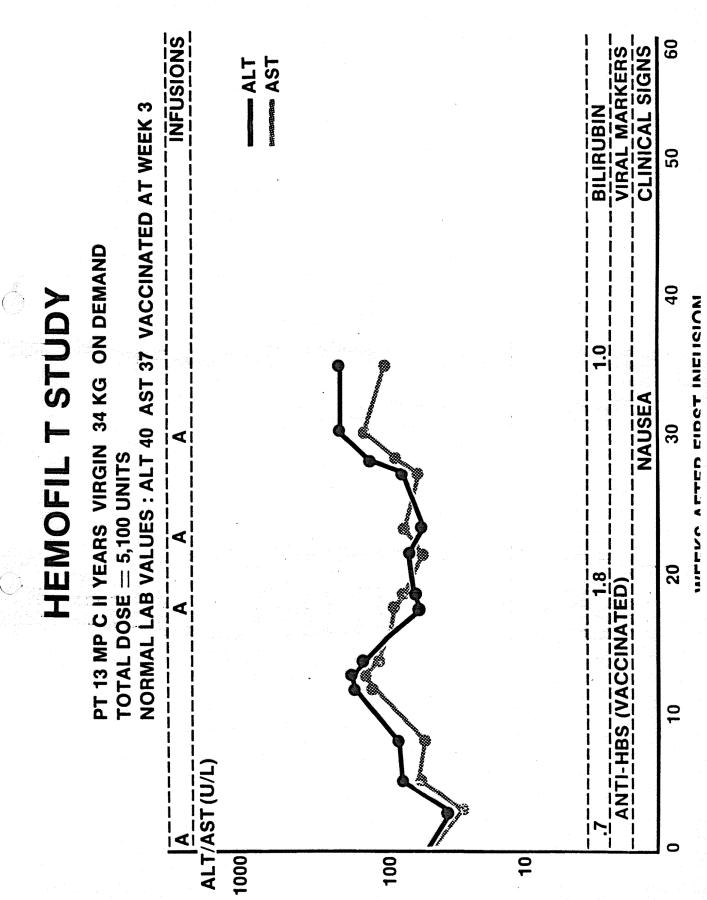


FIGURE 12. 83

INFUSION DATA FOR 14 VIRGIN PATIENTS

PATIENT N°	WEIGHT (kg)	TOTAL DOSE (U)	N° EXPOSURES	U/KG x EXPOSURES
F	10	20,100	67	2,100
7	7	8,750	21	795
5	9	3,000	11	500
7	06	2,600		29
10	10	3,000	4	300
12	50	1,650	<b>**</b>	33
13	34	5,100	Ŋ	150
14	80	22,000		275
15	12	1,260	ŝ	105
16	82	19,980	17	244
17	6	2,130	ო	236
18	20	44,680	10	638
2	9	1,900	S	190
24	12	1,800	9	150
MEDIAN	12	3,000	5.5	240
RANGE	06-9	1,200-44,680	1-67	29-2,100

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HEPATITIS VS. DOSE IN 14 VIRGIN PATIENTS

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f	-		
Total	2	2	14
CMV	•	-	-
No Hepatitis	R	-	4
Hepatitis	4	2	0
Disease status Dose (U/kg x days)	Low <240	High >240	Total

FIGURE 14. 85

## LOTS AND POST TRANSFUSION HEPATITIS (P.T.H.)

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LOT NUMBER P.T.H.	820628A 5/7 (*	820817A 4/6	821123A 0/1	(*) CMV case excluded
LOT	8206	8208	8211	(*)

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FIGURE 15. 86

SUMMARY OF FINDINGS

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### DTH

Attack rate	64 per cent
Type	NANB
Severity	1/9 cases
Lot relationship	Absent
Dose relationship	Absent
ZERO HEPATITIS B (*)	

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(\*) 3/22 patients were vaccinated

### CONCLUDING REMARKS HEMOFIL T CLINICALS

ATTACK RATE REDUCTION = LIKELY, BUT NOT ASSESSABLE

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**I** NONE, SO FAR **EXCELLENT EXCELLENT** SEVERITY REDUCTION **HEPATITIS B** TOLERANCE EFFICACY