INFECTED BLOOD INQUIRY

BRENDON GRAY WITNESS STATEMENT

EXHIBIT WITN6984071

Our Ref MWT/svs

2nd August 1984.

Registration Clerk,
Department of Health & Social Security,
Market Towers,
1, Nine Elms Lane,
Vauxhall,
London,
SW8 5NQ.

Dear Sirs,

CTX NOTIFICATION : KOATE-H.T.

We wish to give notice of a clinical trial and enclose completed form MLA 164 and summaries of data required under SI 1981, No. 164.

Yours faithfully,

Maria W. Tatt (Mrs.),
Registration Manager.

MEDICINES ACT 1968
NOTICE UNDER THE EXEMPTION FROM LICENCES
(CLINICAL TRIALS) ORDER 1981
PART I

1.	Name of Product or designation by which the supplier identifies it:	KOATE-H.T.
2.	Full name and address of person submitting notification:	Miles Laboratories Limited, Stoke Court, Stoke Poges, Slough, SL2 4LY, Berkshire.
3.	Name and address of supplier, if different from 2. above:	
4.	Any other name under which the supplier carries on business:	Cutter Laboratories, Division of Miles Laboratories Limited, Stoke Court, Stoke Poges, Slough, SL2 4LY, Berkshire.
5.	Supplier's reference number:	KHT/1
6.	Details of earlier notices or applications:	
7.	Scientific Evidence:	i. Chemistry and Pharmacy — pages 11-14 ii. Experimental and Biological Studies — pages 15-16 iii. Other studies — pages -

8. I/We hereby give notice of my/our intention to sell or supply, or procure the sale, supply or manufacture or assembly of medicinal products of the description set out in the following pages and summaries for the purposes of a clinical trial. I/We enclose the particulars and summaries required by Article 4(1)(a)(i) of the Medicines (Exemption from Licences) (Clinical Trials) Order 1981.

9. I/We undertake to inform the Licensing Authority of:-

a. any adverse reaction or effects associated with the administration of the medicinal product,

b. any other matter coming to my/our attention which might reasonably cause the licensing authority to think that the medicinal product could no longer be regarded as a product which could safely be administered for the purposes of the clinical trial or as a product which was of satisfactory quality for those purposes,

c. any changes in respect of any of the matters specified in Schedule 2 to the Medicines (Exemption from Licences) (Clinical Trials) Order 1981,

d. any refusal to approve the clinical trial by a Committee established or recognised by a health authority constituted under the National Health Service Act, 1977 or, as the case may be, by a Health Board constituted under either the National Health Service (Scotland) Act 1978 or the Health and Personal Social Services (Northern Ireland) Order 1972 or by the Medical Research Council, to advise on the ethics of research investigations on human beings.

10. Signatures:

Date ..... Name of Supplier ....Miles Laboratories Limited.....

GRO-C

Signature .....

In this notice, the expression "supplier" means a person selling or supplying, or procuring the sale, supply, manufacture or assembly of, a medicinal product for the purposes of a clinical trial.

10.1 I have satisfied myself that the attached summaries are an accurate account of the data obtained by the proposed supplier, and having regard to the content of those summaries, I am of the opinion that it is reasonable for the proposed clinical trial to be undertaken.

Date 18.8.87

Name ..... Dr. B.A. Elliott .....

GRO-C

Signature .....

*Medical Adviser in the employment of

(insert name of proposed supplier)
working at:

Miles Laboratories Limited.

(insert full address and country in which employed)
Stoke Court, Stoke Poges,
Slough, SL2 4LY, Berkshire.

Medical and scientific qualifications:

MB, BCh, BA, MD, FRCPath.

*consultancy to:

(insert name of proposed supplier)
working at:

(address and country in which the consultancy is working)

Medical and scientific qualifications

*delete whichever is inapplicable

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A 1 (Official use only)

Part II

PARTICULARS OF PRODUCT AND TRIAL

Number of Product: (Official use only)

CTX

1. Name of Product and Strength: KOATE-H.T. 250, 500 or 1,000 i.u./vial.

(Official use only)

2. Description of Pharmaceutical form (eg tablets, slow-release tablets, capsules etc):

Lyophilised powder for reconstitution with Water for Injection for intravenous infusion.

(Official use only)

(Official use only)

D 1 (Official use only)

3. Active Constituents:

(Official use only)	Name	Specification Reference	Quantity/Dose Unit or % quantity	Unit
	Coagulation Factor VIII - NLT 0.2 i.u./mg protein The source material is pooled plasma obtained from at least 1000 healthy donors. It is collected by plasmapheresis at centres in the U.S.A. licensed by the FDA and inspected by both the FDA and Cutter Laboratories to ensure compliance with the Code of Federal Regulations. The plasma is collected according to the Cutter System of Plasmapheresis which incorporates all the current FDA requirements for Source Plasma (Human), including testing for Hepatitis B Surface Antigen. In addition, Cutter test samples from all new donors for Antibody to Hepatitis B Core Antigen. This test is also used at four monthly intervals for testing samples from repeat donors. The plasma is immediately frozen after collection and stored in the frozen state until used in production.			

1) Each constituent should be described under a) its approved name or monograph name; o
b) where there is no approved or monograph name, the non-proprietary designation or other descriptive appellation by which it can be readily identified; or c) a laboratory code. 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, th 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 appropriat in unit column. Please do not include percentage sign.
4) Trailing zeros following the decimal point may be omitted eg 10.02 MG will suffice.
5) Please photocopy page if more space for constituents is required.

(Official use only)

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4. **Anticipated clinical use and proposed route(s) of administration:**

The purpose of the study is to investigate the incidence of hepatitis in haemophiliacs following infusion of Koate-H.T.

Route of Administration Intravenous infusion.

(Official Use Only)

B 1 (Official use only)

5. **Proposed dosage range and duration to be used for the trial.**

Dosage

This will be calculated according to the individual patient's requirements as is usual with Factor VIII therapy.

Duration of Trial

9 months study following the patient's first exposure to Koate-H.T.

(Official use only)

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

Cutter Laboratories,
Division of Miles Laboratories Incorporated,
U.S.A.

- Berkeley, California.
- Clayton, North Carolina.

E 1 (Official use only)

7. Other Constituents:

(Official use only)	Name	Specification Reference	mod	Quantity/Dose Unit or % quantity	Unit
	Small amounts of fibrinogen and other				
	plasma proteins. Fibrinogen content is				
	NMT 80% of total protein.				
	Small amounts of the following additives				
	Glycine				
	Normal Serum Albumin				
	Electrolytes				
	Chloride NMT 200mmol/l				
	Sodium NMT 200mmol/l				
	Citrate NMT 55mmol/l				

1) Each constituent should be described under a) its approved name or monograph name; or b) where there is no approved or monograph name, the non-proprietary designation or other descriptive appellation by which it can be readily identified; or c) a laboratory code. 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) Please leave a line between different components of the dosage form, eg. for capsule shell components, coating components.
4) 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.
5) Where quantity is expressed as a percentage please insert WW, WV, etc. as appropriate in unit column. Please do not include percentage sign.
6) Trailing zeros following the decimal point may be omitted eg 10.02 MG will suffice.
7) Please photocopy page if more space for constituents is required.

(Official use only)

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8. **Description of essential processes in the manufacture:**

Cryoprecipitate is recovered by centrifugation from thawed pools of fresh frozen plasma.

Prothrombin complex proteins are removed by adsorption with $Al(OH)_3$.

Extraneous non-Antihaemophilic Factor proteins are removed by chilled acidic precipitation and centrifugation.

The AHF is precipitated with glycine to remove additional extraneous proteins.

The precipitate is solubilised in a buffer at pH 7.0 and the protein is concentrated by diafiltration/ultrafiltration.

The AHF concentrate is diluted as necessary with diafiltration buffer and/or Water for Injection to an acceptable concentration for filling (based on Factor VIII.C assay).

Normal Serum Albumin (Human) is added at NMT 7.5mg/ml for stabilisation.

The bulk solution is filtered through clarifying filters and sterilised by filtration through 0.22µ filters.

The sterile bulk solution is aseptically filled into sterile vials and lyophilised in vacuo.

The freeze-dried product is heated to 68°C for 72-77 hours then stored at 2-8°C.

9. **Finished Product Specification:**

Description : White, lyophilised powder or friable solid.
Factor VIII potency : NLT 14iu/ml when reconstituted with 10, 20 or 40ml distilled water.
Specific activity : NLT 0.8 F VIII units/mg protein.
Solubility : NMT 20 minutes at 20-37°C. No clots of precipitates after 4 hours.
Moisture content : NMT 2%.
pH : 7.0 ± 0.4.
Na+ : NMT 200mmol/l.
Cl : NMT 200mmol/l.
Clarity of solution : Opalescent or slightly yellow.
Safety : Passes test.
Pyrogens : Passes test.
Identity : Human Protein Identity - Passes test
Sterility : Passes test.
Vacuum : Passes test.
Isoagglutinins : Anti A - NMT 1:1024. Anti B - NMT 1:1024.
Citrate : NMT 55mmol/l.
Clottable protein : NMT 2.5% w/v.
HBsAg : Passes test.

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10. Assembler(s): Cutter Laboratories,
Division of Miles Laboratories Incorporated,
U.S.A.

- Berkeley, California & Clayton, North Carolina.

11. Importer: Miles Laboratories Limited,
Stoke Court, Stoke Poges,
Slough, SL2 4LY,
Berkshire.

12. Site and Arrangements for Quality Control:

All quality control will be exercised by the manufacturer, Cutter Laboratories, U.S.A. Miles Laboratories will maintain the necessary documentation to verify acceptable batch quality.

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

Type I clear glass vials with 20mm grey rubber stopper and aluminium seal with plastic flip-off lid.

	Container size	Unit	(Official use only)
Factor VIII concentrate			
250 units	3 0	M L	
500 units	5 0		
1000 units	1 0 0		
Sterile Water for Injection			
10ML, 20ML or 40ML.			
Transfer needle			
16 gauge double-ended stainless steel needle in plastic cover.			
Filter needle			
16 gauge stainless steel needle with aluminium hub in plastic cover.			

Shelf-life

18 months at 2-8°C.

Storage

3 months at RT (25°C). Avoid freezing.

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

PART II B - TRIAL PROTOCOLS

1. **Full details of the proposed trial, together with:**

1.1 names and qualifications of each investigator:

Dr. Peter Jones (Consultant Paediatrician) MD, MB BS, FRCP, DCH RCPS.
Director of Newcastle Haemophilia Centre.

1.2 duration of the trial:

9 months.

1.3 number of patients involved:

The aim is to recruit at least 10 patients.

1.4 criteria used in the selection, exclusion or withdrawal of patients from the trial:

Moderately/mildly affected Haemophilia A patients whose last exposure to blood products was at least six months, before commencing Koate-H.T. trial and in whom DDAVP is thought inappropriate.

In some cases severely affected Haemophilia A patients and patients with Von Willebrands disease could be included provided that their last exposure to blood products was more than six months previously.

If interim results show a high incidence of Hepatitis in the group under investigation the trial will be stopped.

1.5 description of the safety monitoring procedures:

Clinical examination will be confined to physical check-up for evidence of liver disease and full blood counts and liver function tests. The results of any other investigations performed according to individual patients' needs will be recorded.

Tests required
Pre-infusion Hepatitis B markers, full blood counts and liver function tests.

Full blood count and liver function tests will be performed at 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32 and 36 weeks.

Hepatitis B markers will be studied again at 36 weeks.

Simple classification of symptoms and signs of liver disease will be that used by U.K. Haemophilia Directors Hepatitis Survey.

PART III - FURTHER INFORMATION MLA 164

1) Active Constituent

Coagulation Factor VIII obtained by fractionation of normal human plasma.

2) Pharmaceutical Data

2.1. Not applicable since this is a naturally occurring protein.

2.2. Specifications of constituents

Source plasma (human) is collected by plasmapheresis according to the FDA requirements for Source Plasma (Human).

Pooled plasma is obtained from at least 1,000 healthy donors at centres licensed by the FDA and complying with the Code of Federal Regulations. Plasma is collected according to the Cutter System of Plasmapheresis which incorporates all the FDA requirements for Source Plasma (Human). This includes a test on all units of plasma for non-reactivity to a test for Hepatitis B Surface Antigen.

In addition, Cutter test plasma samples from all new donors for Antibody to Hepatitis B Core Antigen. The test is also used at four monthly intervals for testing plasma from repeat donors.

2.3. Quality control procedures

All units of plasma are tested for Hepatitis B Surface Antigen prior to pooling using a radioimmunoassay (AUSRIA).

The method used for testing plasma for Antibody to Hepatitis B Core Antigen is an enzyme linked immunosorbent assay for total gammaglobulin to HBcAg (CORZYME).

All additives are tested for compliance with USP requirements and, in addition, for compliance with the USP test for absence of pyrogens.

2.4. In-process control

Temperature and pH yields are monitored throughout the process. Since this is a continuous process no other analytical tests are carried out apart from the A_{280} assay which is performed on a sample taken after solubilisation of the cryoprecipitate and during the ultrafiltration process.

Buffers are tested for pH, specific conductivity and pyrogens prior to use.

Monitoring for microbiological contamination is performed periodically throughout the production process and the plasma, fractionation supernatants and additive solutions are maintained at the lowest possible temperatures consistent with processing requirements.

NOTE :The nature of the product is such that the entire process must be carried out to final container without stopping and therefore tests are not carried out on the bulk solution. All analytical tests are carried out on the freeze-dried and heat-treated product immediately after reconstitution with Sterile Water for Injection.

2.5. Stability

Stability studies of Koate-H.T. have been conducted on batch S 8505 (1,000 units approximately) stored in 100ml Type I clear glass vials with grey rubber stopper, plastic cap and aluminium seal.

Samples of this batch have been stored at 3 months at 5°C and 25°C. The results show no significant change in physical or biological tests at the end of this period and are considered adequate to support at least an 18 months shelf-life at 5°C and 3 months if stored at Room Temperature.

The tests performed and results are tabulated below:-

TEST		INITIAL	3 MONTHS
Factor VIII activity (u/vial) (partial thromblastin time)	5°	1188	1224
	25°	1188	1340
Specific activity (u/mg protein)	5°	1.1	Not done
	25°	1.1	1.3
pH	5°	7.2	7.2
	25°	7.2	7.3
Clarity (% T580 NM)	5°	91.8	92.2
	25°	91.8	92.5
Moisture (%) (loss on drying - Alberhalden vacuum drying apparatus)	5°	0.5	1.2
	25°	0.5	1.2
Appearance	5°	opalescent/ slightly yellow	opalescent/ slightly yellow
	25°		
Solubility (minutes)	5°	2	6
	25°	2	6
Vacuum test	5°	passes	passes
	25°	passes	passes

Bioavailability

In-vivo studies have demonstrated that the half-life and recovery of Factor VIII is similar to the non-heat-treated product.

2.6. The methods to be employed during manufacture for determining the identity, purity and potency of the product

All procedures are carried out by Cutter Laboratories at their manufacturing premises in Berkeley or Clayton, U.S.A.

2.6.1. Finished Product Specification

Description	:	White, lyophilised powder or friable solid.
Factor VIII activity (partial thromblastin time using in-house standard calibrated against the WHO Third International Standard for Factor VIII C)	:	NLT 14 iu/ml when reconstituted with 10ml, 20ml or 40ml distilled water.
Specific activity (calculated from protein content)	:	NLT 0.8 F VIII units/mg protein.
Solubility (solution time and appearance)	:	NMT 20 minutes at 20-37°C. No clots or precipitates after 4 hours.
Moisture content (L.O.D. using vacuum drying apparatus)	:	NMT 2%.
pH	:	7.0 ± 0.4
Sodium content (Atomic absorption spectrophotometry)	:	NMT 200mmol/l.
Chloride content (Titration using Corning Chloride meter)	:	NMT 200mmol/l.
Clarity (visual)	:	Opalescent or slightly yellow.
Safety test (7 day test in mice and guinea pigs. FDA approved. 21 CFR 610.11)	:	Passes test.
Pyrogens (USP Pyrogen test)	:	Passes test
Identity (Precipitin test for human protein)	:	NLT 15 i.u. AHF/ml.
	:	Passes test.

Sterility (FDA approved test. 21 CFR 610.12)	: Passes test
Vacuum (Spark test)	: Passes test
HB_sAg (radioimmunoassay)	: Passes test.
Isoagglutinins (saline/saline	: NMT 1:1024
-Coombs test)	: NMT 1:1024
Citrate content (Absorption spectrophotometry)	: NMT 55 millimoles/l
Clottable protein (cellulose acetate electrophoresis)	: NMT 2.5% w/v.

2.7. Not applicable. No other products will be used in the clinical trial.

3. Experimental and Biological Studies

3.1. Virus inactivation studies

Samples of selected virus cultures were added to pre-lyophilisation samples of Antihaemophilic Factor (Koate). Following lyophilisation and incubation at 68°C for 72 hours the following results were obtained:-

Vesicular stomatis virus was completely inactivated within 24 hours.

Vaccinia virus and porcine virus titres were reduced by 1.3 - 2.0 logs after 72 hours.

Cytomegalovirus was completely inactivated in 10 hours.

Herpes simplex virus type I was completely inactivated in two hours.

Sindbis virus was completely inactivated within 72 hours.

The results demonstrate that selected viruses are inactivated by the Koate-H.T. process and by inference other viruses may also be inactivated.

3.2. Lack of Effect of Heat-Treatment on Antihaemophilic Factor

In-vitro immunological evaluation to investigate formation of neo-antigens and fragmentation products using SDS-PAGE Electrophoresis, Gel Permeation Chromatography, Immunodiffusion and Crossed Immunoelectrophoresis demonstrated that heat-treatment does not detrimentally alter Koate.

A one month repeated dose toxicity study in groups of male New Zealand white rabbits demonstrated no adverse effects of Koate-H.T. with regard to body weight gain, haematology, blood chemistry, necropsy or histology.

Groups were administered:-

a) Koate-H.T.
b) Koate (not heated)
c) Vehicle control

Five successive days of I.V. infusions of 3.0ml/kg of each test substance were followed by:-

a) Sacrifice in one group of 5 animals.

b) a month observation period followed by sacrifice in a second group of 5 animals.

The control groups received an aqueous solution of additives present in Koate-H.T. without the protein and

groups were sacrificed after five days or 1 month later.

The results for both the control groups and the non-heat-treated Koate groups were comparable to those for Koate-H.T.

It was concluded that dry heat-treatment does not adversely affect the product.

3.3. Biological half-life and in-vivo recovery

The in-vivo recovery and half-life of Koate H.T. was determined in six non-bleeding subjects with Haemophilia A.

The Factor VIII recovery after infusion of 50iu/kg was 98.2%, representing an average rise of 1.96% for each unit/kg infused.

A biphasic survival curve was demonstrated with a first phase distribution half-life of 5.3 hours and a second phase biologic half-life of 10.2 hours.

These values are similar to published literature values for Factor VIII preparations and to those reported in our product licence application for non-heat-treated Koate. The initial 50% disappearance time for Koate was 5 hours with a mean biologic half-life of 12.7 hours.