Bayer

Bayer UK Limited
Pharmaceutical Business Group
Bayer House
Strawberry Hill
Newbury
Berkshire
RG13 1JA

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Department of Health,
Medicines Control Agency,
Renewals Section,
Market Towers,
1 Nine Elms Lane,
LONDON SW8 5NQ

Your ref

Our ref CDS/ER/174

Date 2 November 1989

Dear Sirs,

APPLICATION TO RENEW PL 0055/0107 FOR KOATE HT

The above licence is due to expire on 17 February 1990. Thus, please find enclosed an application to renew this licence (MLA 231 - 4 copies).

Yours faithfully,

GRO-C

Craig D. Simpson
SENIOR REGISTRATION OFFICER

encs.

APPLICATION FOR
RENEWAL OF PRODUCT LICENCE

Form MLA 231 (Revised 1/4/89)

MEDICINES ACT 1968, 1971

A a. Full name and address of licence holder: Miles Limited, Stoke Court, Stoke Poges, Slough, Berkshire, SL2 4LY

b. Trading style to be shown on licence if different from above: N/A

B Particulars of Present Licence:

(i) Number: PL 0055/0107

(ii) Name of Product: Koate HT

(iii) Date Granted: 18 February 1985

(iv) Date of Expiry: 17 February 1990

(v)* Is this product currently on the UK market? YES/~~NO~~[1]

C a) Dates of approval of change(s)[2] in the original particulars: 31.7.85 (2), 23.1.86, 3.6.88, 3.10.88, 27.2.89 (3).

b) Dates of applications for change(s)[2] not yet determined: NIL

D Other than the changes referred to in C, ~~I am/am not~~[1]/we ~~are~~/are not[1] seeking additional change(s) to the product licence described above in this renewal application.

The reason(s) for the change(s) to the licence is/are set out in the attached MLA 221. N/A

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

NIL

F

Renewal Fee Payable ☑ POM Product ☐ PL(PI) ☐ PLR ☐ Other

Please tick the appropriate box

I/We[1] apply for the renewal of the product licence described above for a period of five years from the date of expiry given above.

I/We[1] have specified all the changes to the product licence described above that I/We[1] wish to make by this application, together with the reason(s) for the change(s) which is/are contained in Form MLA 221 dated .....N/A.....[3] attached.

I apply for the product licence to be renewed in accordance with the particulars given above and any accompanying documents, and any given in the original application as amended by the changes referred to in C above. The licence shall further be subject to all provisions of the existing licences now in force.

Date: 30 October 1989 Signature: GRO-C - Craig Simpson

State capacity in which signed: Senior Registration Officer
On behalf of Miles Limited

Tel. GRO-C

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

Name and address for communications: (if different from above)
Mr. C. Simpson, Senior Registration Officer,
Bayer UK Limited, Bayer House, Strawberry Hill, Newbury, Berkshire, RG13 1JA

Notes 1. Delete as applicable. 2. Change means variation. 3. Please complete.
* This information is requested for statistical purposes only.

(Official use only)

A 1 /

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

Number of Product: (Official use only)

PL /

1. Name of Product and Strength: Koate HT, 250, 500, 1000, 1500 IU FACTOR VIII

(Official Use Only)

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

Koate HT is a white lyophilised powder presented in vials containing approximately 250, 500, 1000, and 1500 International Units of Factor VIII, for reconstitution with Water for Injection.

(Official use only)

(Official use only)

3a. Legal status requested (place tick in appropriate box(es))

(Official use only)

Prescription	Pharmacy	General Sales	Not applicable
✓			

3b. Method of retail sale or supply: To haemophilia centres as a prescription item.

(Official use only)

Text should be completed in block capitals.

Date: 30 October 1989

(Official use only)

D	1						/									

4. Active Constituents:

(Official use only)	Name	Specification Reference	Quantity/Dose Unit or % quantity	Unit
	Coagulation Factor VIII - NLT 0.8 i.u./mg protein The source material is pooled plasma obtained from at least 1,000 healthy donors. It is collected by plasmapheresis at centres in the USA, 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 and antibodies for HIV. 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.			

Details of any overages:- These should not be included in the formulation columns but stated in this section.

1) Please enter constituent(s) as actual substances included in the formulation, eg as salt and then as base equivalent where applicable.
2) See page E1, paragraph 2 for approved abbreviations
Where a specification 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) In the case of liquid preparations: all quantities for oral preparations should relate to a 5ml dosage. Please state in dosage information any deviation from this rule. Quantity should be expressed as a percentage for other liquid preparations, included parenterals. Please insert WW,WV etc. as appropriate in the Unit Column. DO NOT INSERT a percentage sign; this is automatically inserted by computer.
4) The following abbreviations for units are recommended:
NG nonogrammes; UG micrograms; MG milligrams; GM grammes; KG kilogrammes; UL microlitres; ML millilitres; L litres; U units; KU kilounits; MU megaunits; I.U. international units; UC microcuries; BC becquerels.
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.

Date: 30 October 1989

C 1 (Official use only) /

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

Indications

The treatment of classical haemophilia (haemophilia A) in which there is a demonstrated deficiency of Factor VIII activity.

Route of administration

Intravenous infusion.

(Official use only)

All entries must be made in full. Cross references, eg to accompanying data sheets are not acceptable.

Date: 30 October 1989

(Official use only)

B 1 / [ ]

6. Recommended doses and dosage schedules

[ ] (Official use only)

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

Dosage

The following formulae provide a guide for dosage calculations:

Expected Factor VIII increase (in % of normal)

$$= \frac{\text{IU administered} \times 2.0}{\text{Bodyweight (in kg)}}$$

IU required = Bodyweight (kg) x desired Factor VIII (% normal) x 0.5

All efforts should be made to follow the course of therapy with Factor VIII level assays. It may be dangerous to assume any certain level has been reached unless direct evidence is obtained.

(Official use only)

Date: 30 October 1989

(Official use only)

B 1 /

7. Contraindications, Precautions and Warnings listed, with titles, in the following order:

a) Contraindications
b) Interactions with other medicaments and other forms of interaction
c) Effects on ability to drive and to use machines
d) Other undesirable effects (frequency and seriousness)
e) Use in pregnancy and lactation
f) Other special warnings and precautions
g) Overdose (symptoms, emergency procedures, antidotes)
h) Incompatibilities (major)

a) Contraindications

There are no specific contraindications to the use of Koate HT.

b) Interactions with other medicaments and other forms of interaction

None stated.

c) Effects on ability to drive and operate machinery

None stated.

d) Other undesirable effects

1. Allergic reactions including chills, fever, and hypersensitivity reactions may result from the administration of Factor VIII preparations.

2. When large or frequently repeated doses are required in patients of blood groups A, B, or AB, there is a possibility of intravascular haemolysis. Should this condition occur leading to progressive anaemia, administration of serologically compatible red blood cells should be considered. Also, the administration of type specific cryoprecipitate has been recommended for maintaining adequate Factor VIII levels.

3. Massive doses of Factor VIII preparations may result in hyperfibrogenaemia.

4. Koate HT concentrate is a purified fraction of pooled plasma obtained from many donors. The presence of hepatitis viruses should be assumed and the hazard of administering Koate HT should be weighed against the medical consequence of witholding it, particularly in persons who have had few previous transfusions of blood or blood products.

continued/

(Official use only)

Date: 30 October 1989

B 1 (Official use only)

7. Contraindications, Precautions and Warnings listed, with titles, in the following order:

a) Contraindications
b) Interactions with other medicaments and other forms of interaction
c) Effects on ability to drive and to use machines
d) Other undesirable effects (frequency and seriousness)
e) Use in pregnancy and lactation
f) Other special warnings and precautions
g) Overdose (symptoms, emergency procedures, antidotes)
h) Incompatibilities (major)

e) Use in pregnancy and lactation

None stated.

f) Other special warnings and precautions

1. Koate HT is intended for the treatment of bleeding disorders arising from a deficiency of Factor VIII. This deficiency should be proven prior to administering Koate HT, since no benefit may be expected from its use in treating other causes of haemorrhage.

2. After reconstitution, administer as promptly as possible and within 3 hours. Do not refrigerate after reconstitution.

   Note: The recommendation to administer promptly after reconstitution is intended to avoid the ill effect of any possible bacterial contamination occurring during reconstitution. Koate HT, in the vial unopened, is sterile. It is fully stable, without potency loss for at least 24 hours at room temperature after reconstitution.

3. Administer only by the intravenous route.

4. A filter needle should always be used for transfer to syringe prior to administering.

5. Koate HT contains levels of blood group isoagglutinins which are not clinically significant when controlling minor bleeding episodes. When large or frequently repeated doses are required in patients of blood groups A, B, or AB, the possibility of onset of intravascular haemolysis should be considered.

6. Administration equipment and any reconstituted Koate HT not used should be discarded.

(Official use only)

Date: 30 October 1989

E 1 (Official use only) /

8. 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 not more than 80% of				
	total protein.				
	Small amount of the following				
	additive: Glycine				
	Electrolytes:				
	Chloride NMT 200 mmol/l				
	Sodium NMT 200 mmol/l				
	Citrate NMT 50 mmol/l				

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) Recommended abbreviation for units are given on page D1, paragraph 4.
5) In the case of liquid preparations: all quantities for oral preparations should related to a 5ml dosage. Please state in dosage information any deviation from this rule. Quantity should be expressed as a percentage for other liquid preparations, including parenterals. Please insert WW, WV, etc as appropriate in the unit column. DO NOT INSERT a percentage sign; this is automatically inserted by computer.
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.

Date: 30 October 1989

H 1 (Official use only)

9. Description of essential processes in 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.

10. Finished Product Specification:

Description:	White, lyophilised powder or friable solid.
Factor VIII potency:	NLT 14 IU/ml when reconstituted with 10, 20 or 40ml distilled water.
Specific activity:	NLT 0.8 Factor VIII units/mg protein.
Solubility:	NMT 20 minutes at 20-37°C. No clots or precipitates after 4 hours.
Moisture content:	NMT 2%.
pH:	7.0 ± 0.4.
Na+:	NMT 200 mmol/l (145 - 185 mEq/l).
Cl:	NMT 200 mmol/l (125 - 160 mEq/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 55 mmol/l.
Clottable protein:	NMT 2.5% w/v.
HBsAg:	Passes test.

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(Official use only)

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11. Arrangements for storage and address(es) of storage premises:

The product will be stored at 2-8°C, segregated from other materials, at
Bayer UK Limited,
Central Warehouse, Shaw Lane,
Stoke Works,
Bromsgrove, Worcestershire, B60 4EA

12. Special precautions for storage:

Store at 2-8°C. Do not freeze.

13. Nature of container and closure

Factor VIII concentrate

		Shelf-life(A)	Shelf-life(B)	Pack Size
Type 1 clear glass vial with 20mm grey rubber stoppers, aluminium seals and plastic flip-off cap.	250 units	24M	1D	30
	500 units	24M	1D	50
	1000 & 1500 units	24M	1D	100

Sterile Water for Injection

	Shelf-life(A)	Shelf-life(B)	Pack Size
Type 1 clear glass vials with 20mm grey rubber stoppers, aluminium seals and plastic flip-off cap.	24M		20
	24M		30
	24M		50

NOTE: The above shelf-life (A) terms are for product stored at 2-8°C. Shelf-life (B) refers to the reconstituted product at room temperature.

Unit: ML

Notes:

1) Shelf-life should be expressed in months (M), weeks (W), or days (D) as appropriate eg 3 6 M

A = Unopened
B = After reconstitution or when the container is opened for the first time, if appropriate.

2) The pack size should contain numbers only, right aligned. If a decimal point is required it should occupy one box.

3) Where applicable enter the unit of measure as MG, GM, ML, LT in the Unit box . No entry is required in the Unit box for solid dosage forms.

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K 1 (Official use only) /

14. Pharmacological particulars:

In individuals suffering from haemophilia A, haemorrhages may occur spontaneously or after only minor trauma. Surgery on such individuals is not feasible without first correcting the clotting abnormality. The administration of Koate HT provides an increase in plasma levels of Factor VIII and can temporarily correct the coagulation defect in these patients.

15. Pharmacokinetic particulars:

After infusion of antihaemophilic factor (AHF), there is usually an instantaneous rise in the coagulant level, followed by an initial rapid decrease in activity, and then a subsequent much slower rate of decrease in activity. The early rapid phase may represent the time of equilibration with the extravascular compartment, and the second or slow phase of the survival curve presumably is the result of degradation and reflects the true biologic half-life of the infused AHF.

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(Official use only)

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16. Name(s) of manufacturers and site(s) of manufacture of (a) the active substance(s) and (b) the dosage form

The active substance and The dosage form

a) All manufacturing and assembly operations for Koate HT (lyophilised Factor VIII):

Cutter Biological
Division of Miles Inc., USA
- Berkeley, California, USA
- Clayton, North Carolina, USA

b) Sterile Water for Injection:

Hollister-Stier, PO Box 3145 Terminal Annex, North 3525 Regal Street, Spokane, Washington 99207, USA.

17. Assembler(s):

As in 16.
In addition, Koate HT may be re-labelled and re-packaged by Miles Limited, Western Avenue, Bridgend Industrial Estate, Bridgend, Glamorgan, South Wales.

18. Importer

The licence holder:
Miles Limited,
Stoke Court,
Stoke Poges,
Slough, Berkshire
SL2 4LY

19. Site and arrangements for quality control:

The manufacturer, Cutter Biological USA, will be responsible for all quality control of the raw materials and finished product at Berkeley, California, and Clayton, North Carolina. Miles Limited, Bridgend, Glamorgan, South Wales, will maintain the necessary documentation and verify that each batch of the product is acceptable for release in the UK. Miles Limited will also be responsible for Q.C. operations associated with any re-packaging or re-labelling activities (detailed in section 17). All batches of Water for Injection will, following importation, be tested and must comply with the BP prior to release. Testing will be carried out by Miles Limited, Bridgend, Glamorgan, South Wales.

20. Distributor (where applicable):

Cutter Biological,
Bayer House,
Strawberry Hill,
Newbury, Berkshire,
RG13 1JA

21. List other countries of registration:

USA, West Germany.

Date: 30 October 1989