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

Telephone: Newbury (0635) 39000 Direct dialling: Newbury (0635) 39. 285 Fax: (0635) 39404 Telex: 847205 Baynew G

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

Your ref

CDS/ER/174

Date 2 November 1989

Dear Sirs,

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APPLICATION TO RENEW PL 0055/0107 FOR KOATE HT

Our ref

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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.

Directors: M. Schneider, Chairman, J.V. Webb, Managing, R. Korn, Lord Walston Company registered in England No. 935048 Registered Office Bayer House Newbury Berkshire RG13 1JA

APPLICATION FOR

RENEWAL OF PRODUCT LICENCE

Form MLA 231 (Revised 1/4/89) Page 1

MEDICINES ACT 1968, 1971 A Full name and address a. Miles Limited, of licence holder: Stoke Court, Stoke Poges, Slough, Berkshire, SL2 4LY Trading style to be shown Ъ. on licence if different from above: N/A Particulars of Present Licence: В (i) Number: PL 0055/0107 (ii) Name of Product: Koate HT (iii) Date Granted: 18 February 1985 (iv) Date of Expiry: 17 February 1990 Is this product currently on the UK market? (v)* YES/XOL a) Dates of approval of change(s)² in the original particulars: С 31.7.85 (2), 23.1.86, 3.6.88, 3.10.88, 27.2.89 (3). b) Dates of applications for change(s) not yet determined: NIL Other than the changes referred to in C, $\frac{1-am/am-not^{1}}{1-am/am-not^{1}}$ /we are/are not seeking D additional change(s) to the product licence described above in this renewal The reason(s) for the change(s) to the licence is/are set out in the attached If any further documents are attached, give number of pages and a brief Е NIL F POM Product PL(PI) Renewal Fee Payable PLR Other Please tick the appropriate box χ'/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. χ/We_1^1 have specified all the changes to the product licence described above that χ/We_1^1 wish to make by this application, together with the reason(s) for the change(s) which is/are contained in Form MLA 221 datedN/A..... 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 **GRO-C** - Craig Simpson Signature: 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.

MLA 231 Page 2-
A 1 (Official use only)
FRODUCT 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): presented in vials containing approximately (Official use only) 250, 500, 1000, and 1500 International Units of Factor VIII, for reconstitution with Water for Injection.
(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

D 1	(Official use only)	Τ			[NL4	1 23	1	Pag	e
4. Activ (Official use only)	ve Constituents: Name	ic	ati	f- on enc	U	nit	or	Dos ity		Un	it
	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-						<u> </u>				
	- 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 				 			-			
	requirements for Source Plasma (Human), including testing for Hepatitic B Sumface					 					
	addition, Cutter test samples from all new donors for Antibody to Hepatitic P										-
++++	Core Antigen. This test is also used at four monthly intervals for testing samples from repeat donors.					—i					
	The plasma is immediately frozen after collection and stored in the frozen state until used in production.				 	;			-		
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 $^{|}_{\gamma}$ Details of any overages:- These should not be included in the formulation columns but

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.

		(Of	ficial use on	ly)		MLA 231 Pag
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5.	Recommended c	linical ind	ications and	· · · · · · · · · · · · · · · · · · ·		
	route(s) of a	Idministrati	on:			
	Indications					
	The treatment demonstrated of	of classica deficiency c	al haemophilia of Factor VIII	a (haemophilia activity.	A) in which t	here is a
	Route of admin	nistration				
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are not acceptable.

B 1 (Official use only)	
6. Recommended doses and dosage schedules	(Officia)
Distinguish between adults, children and the elderly and between different indications	use only
Dosage	
The following formulae provide a guide for dosage calculations:	
Expected Factor VIII increase (in % of normal)	
= IU administered x 2.0	
Bodyweight (in kg)	
IU required = Bodyweight (1-g) a desired =	والمتركبة فتقاد الأشار ال
IU required = Bodyweight (kg) x desired Factor VIII (% normal)	x 0.5
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Date: 30 October 1989

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, se considered.		3. 4. 5. F	prior its us After 3 hour <u>Note</u> : Adminis Adminis Coate H linica	to ad e in recon s. D The is is cont. vial loss recon ster o ster o ster in terin T con	Iminis treat stitu o not recom ntenda amina unopo for a nstitu only h edle s ng. stains	teri ing tion ref mend ed t tion ened at la ution by th shoul	ng otl , ; atio atio eas n. he ld	Koata her ca admini gerate ion to avoid curri s ste t 24 intra alway s of 1	e HT ause ste add the rile hour vence s be	y, s s o r a ter min il dur e. rs a ous e us od g	ince f had s pro reco ister l eff ing r It i at ro rout ed f	no emor pompt fonst: for fect fecor s fu e. or t iso	ly a itut of sti illy cempo	sfer	y show may f ossibl fter possi on. ble, ure a to s	uld b be ex le an reco ble Koat Koat fter yring which	pe provo pected d within nstitut bacteri e HT, i out pot ge prio	<pre>in from in al n th ency</pre>
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E 1													
8. Otl	her Constituents:												
(Officia use only	7) Name	ica	ecif atio fere	n	mo	1.		anti Unit % qu	or			Un	it
	Small amounts of fibrinogen and						T		1				T
	other plasma proteins. Fibrinogen		1-				+-	+			۲. د در		_
	content is not more than 80% of							-	i	- 1 - 1 - 1 			<u> </u>
	total protein.							-	-				
		$\left \right $				+	-						
$\left \right $	Small amount of the following	-				+-						\neg	
╎╷╷	additive: Glycine			-				-i	-		-		
				-+		+				\rightarrow	-	-	
	Electrolytes:	·		-+-		+			-				
	Chloride NMT 200 mmol/1			-+-	·	┼─						+	
·	Sodium NMT 200 mmol/1		\rightarrow				$\left - \right $				+	+	
	Citrate NMT 50 mmo1/1					+					+		
			+		+	$\left - \right $		— <u>i</u> -	<u>.</u>		+	_	<u> </u>
				+	+						╀	+	
		-+	F	+-		┠─┤	\rightarrow	- i -	-			+-	\neg

- r) 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 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.

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	9. Description of esse	ential processes in manufacture:
	<u>Cryoprecipitate</u> is	recovered by centrifugation from thawed pools of fresh
	<u>Prothrombin</u> complex	proteins are removed by adsorption with Al(OH)3.
	<u>Extraneous</u> non-anti precivit	haemophilic factor proteins are removed by chilled acidic ation and centrifugation.
	The AHF is precipit	ated with glycine to remove additional extraneous proteins.
	<u>ine precipitate</u> is con	solubilised in a buffer at pH 7.0 and the protein is centrated by diafiltration/ultrafiltration.
	The AHF concentrate	is diluted as necessary with diafiltration buffer and/or njection to an acceptable concentration for filling (based III C assay).
	Normal serum albumir	(human) is added at NMT 7.5mg/ml for stabilisation.
	The bulk solution is	filtered through clarifying filters and sterilised by ltration through 0.22μ filters.
	The sterile bulk sol	ution is aseptically filled into sterile vials and lyophilised in vacuo.
	The freeze dried pro	duct is heated to 68°C for 72-77 hours, then stored at 2-8°C.
10	. Finished Product Spe	
	Description:	
k. Ng	Factor VIII potency:	White, lyophilised powder or friable solid.
Ĵ		NLT 14 IU/ml when reconstituted with 10, 20 or 40ml distilled water.
	Specific activity: Solubility:	NLT 0.8 Factor VIII units/mg protoin
•	conductiv:	min 20 minutes at 20-37 C
	Moisture content:	No clots or precipitates after 4 hours. NMT 2%.
	pH: Na+:	7.0 ± 0.4 .
	Na+: C1:	NMT 200 mmol/1 (145 - 185 mEq/1).
	Clarity of solution:	$\frac{1}{125} - \frac{160}{160} \frac{1}{125} - \frac{160}{10} \frac{1}{10}$
	Safety:	Opalescent or slightly yellow. Passes test.
	Pyrogens:	Passes test.
	Identity: Sterility:	Human protein identity - passes test.
	Vacuum:	Passes test. Passes test.
	Isoagglutinins:	
	Citrate:	NMT 55 mmo1/1.
	Clottable protein: HBsAg:	NMT 2.5% w/v.
	0.	Passes test.

	(Official use only)
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11. Art	rangements for storage and address(es) of storage premises:
The	product will be stored at 2-9°C
Bay Cen	e product will be stored at 2-8°C, segregated from other materials, at tral Warehouse, Shaw Lane,
3.0	Ke works.
	msgrove, Worcestershire, B60 4EA
	cial precautions for storage:
Sto	re at 2-8°C. Do not freeze.
<u></u>	
13. Natu <u>Fact</u>	re of container and closure for VIII concentrate
	Shelf-life(A) Shelf-life(B) Pack Size
vial	with 20mm grey
alum	inium seals and 500 units 2 4 M 1 D
plas	tic flip-off cap.
	1000 & 1500 units 2 4 M 1 D 1 D
Ster	ile Water for Injection
with	1 clear glass vials 2 4 M 2 0 20mm grey rubber 2 0
stop	pers, aluminium seals 2 4 M 3 0
	2 4 M 5 0
NOTE:	The above shelf-life (A) terms are Unit for product stored at 2-8°C. Shelf-life (B) refers to the reconstituted product at room temperature.
otes: 1)	appropriate eg $A = Unopened$
	3 6 M 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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14	. Pharm	acologic	al particular	-			
	In in spont not f admin	dividuals aneously easible v istration	s suffering f or after onl without first	from haemoph ly minor tra correcting	the clotti	morrhages may ry on such in ng abnormalit in plasma lev ılation defec	dividuals is
				•			
5 .	Pharma	cokinetic	particulars	:			
	in acti with th surviva	se in act vity. The extravation	ivity, and the early rap	hen a subsec id phase may artment, and	quent much s represent the second	tere is usual d by an initi- lower rate of the time of e or slow phas tion and refl	al rapid decrease quilibration
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16.	manufacturers and sito(c)	of manufacture
	substance(s) and (b) the dosage form	or manufacture of (a) the active
	The active substance and	f mt 1
- 1		The dosage totill
d j) All manufacturing and assembly operati	ons for Koate HT (lyophilised Factor V
	Cutter Biological	
	Division of Miles Inc., USA	
	- Berkeley, California, USA - Clayton, North Carolina, USA	
Ъ١		는 전체에서 관계되었다. 2012년 2013년 2013년 1월 201 1월 2013년 1월 2
U)	Sterile Water for Injection:	
	Hollister-Stier, PO Box 3145 Terminal Spokane, Washington 99207 USA	Annex, North 3525 Regal Street
	Spokane, Washington 99207, USA.	in the court offer,
17.	Assembler(s):	18. Importer
	As in 16.	The licence holder:
	In addition, Koate HT may be	Miles Limited,
	re-labelled and re-packaged by Miles Limited, Western Avenue,	Stoke Court,
	Bridgend Industrial Estate,	Stoke Poges,
	Bridgend, Glamorgan, South Wales.	Slough, Berkshire SL2 4LY
19.	Site and arrangements for quality cont	
	The manufacturer, Cutter Biological US	SA, will be responsible for all quality
	and Clayton, North Carolina, Miles Li	mitod Priderad al
•		
	following importation, he tested and m	All batches of Water for Injection wil
	Testing will be carried out by Miles L	imited, Bridgend, Glamorgan, South Val
20.	Distributor (where applicable):	
	Cutter Biological, Bayer House,	
	Strawberry Hill,	
	Newbury, Berkshire,	
	RG13 1JA	
0.1		
21.	List other countries of registration:	
21.	List other countries of registration: USA, West Germany.	

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