NOT FOR PUBLICATION

COMMERCIAL IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

SUB-COMMITTEE ON BIOLOGICAL PRODUCTS

Minutes of the meeting held on 7 March 1984

PRESENT

[redacted] (Chairman)
[redacted]
[redacted] (Medical Assessor)
[redacted] (Pharmaceutical Assessor)
[redacted] (Secretary)

ALSO PRESENT

[redacted]) NIBSC
[redacted]) NIBSC
[redacted]) NIBSC
[redacted] MAFF
[redacted]

1. Confidentiality and Announcements

The Chairman welcomed [redacted] who was attending the meeting for the first time. He also welcomed [redacted] who had recently been appointed Medical Assessor to the Sub-Committee, and [redacted] who recently became Secretary to the CSM.

The Chairman reminded members that the material they received was confidential and should not be disclosed outside the meeting. He also reminded members that any interest in applications under consideration should be declared before they were discussed by the Sub-Committee.

2. Apologies for absence

An apology for absence had been received from [redacted].

3. Minutes of the meeting held on 4 January 1984

These were agreed and signed by the Chairman as a correct record of the proceedings.

4. Matters arising from the minutes

The Sub-Committee noted the CSM's advice on applications previously considered by the Sub-Committee. The Chairman drew member's attention to the CSM's advice on the applications for Solcotrichovac and Berofor Nasal Spray.

The Sub-Committee had recommended the issue of a clinical trial certificate for Berofor Nasal Spray, as had the CPS Sub-Committee, both with a number of conditions. The CSM had considered that there were too many conditions for the professional Secretariat to clear with the Company within a reasonable time period.

In respect of Solcotrichovac, CSM had asked SEAR to consider the application, particularly with respect to the clinical trial data. SEAR had considered that further clinical trial evidence of safety and efficacy was required, a view which CSM had endorsed.

CSM had advised that Section 21(1) action should be taken on both applications.

5. Consideration of applications

5.1 PL/3070/0007 - Speywood Industries - Hyate:C

5.2 PL/0086/0100 - Hoechst UK Ltd - Factor VIII HS

5.3 PL/0022/0056 - KabiVitrum Ltd - Gammonativ

The Sub-Committee's recommendations on these applications are at appendices A-C.

6. Written representation

PL/0093/0046-7 - Servier Laboratories Ltd - Tetavax.

The Sub-Committee's recommendation on this written representation is at appendix D.

7. Paper : Consideration for the Standardization and Control of the New Generation of Biological Products

The Sub-Committee endorsed this paper, which had been prepared by NIBSC, and recommended that it be presented for consideration by CSM at their next meeting.

8. Item for information - MAIL 39

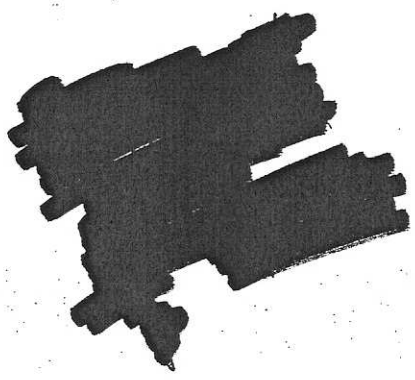
This was circulated to members for their information.

9. Any other business

None.

10. Date and time of next meeting

Wednesday, 2 May 1984 at 10.30 a.m.



No.

PL/3070/0007

Coy.

Speywood Laboratories Ltd

Product

Hyate: C

Therapeutic Class

Blood Product

Active Constituent

Porcine Factor VIII:C

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RECOMMENDATION

On the evidence before them the Sub-Committee, on grounds of safety and quality, were unable to recommend the grant of a Product Licence for this product.

The Sub-Committee considered that:

1. there was insufficient evidence of safety in long-term use for the propylamine extractables present in the product,

2. the Company should justify the aluminium levels in the finished product and demonstrate that these levels do not provide a toxic hazard in clinical use,

3. clarification should be provided on certain aspects of the manufacturing process, with particular reference to: blood collection; initial processing; sterilisation of plastic bags; changes made to the manufacturing/control processes and Finished Product Specifications over the period of time the product has been in clinical use; the choice of molar ratio used in the polyelectrolyte; and on the in process levels of extractables,

4. full details should be provided of the Factor VIII standards used in the assay of the product, that is both the "in-house" standard and that supplied by Diagnostic Reagents Ltd.,

5. data from the accelerated stability study should be provided along with details of how these and standard stability tests on an on-going basis will be undertaken,

6. justification should be provided for the limits applied to:

i) Factor VIII:C activity,
ii) Platelet aggregating activity,
iii) Residual polyethylene glycol,
iv) Aluminium

Remarks

1. in the event of a Product Licence being granted the Sub-Committee considered that:

1.1 the licence should be conditional on satisfactory inspection reports from the factory and the abbatoir, with particular reference to the use of the proposed blood collection technology,

1.2 the Company should be encouraged to set up post-marketing surveillance studies to monitor the long-term safety of Hyate: C,

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1.3 a full stop-on-sale order should be applied to all batches of the product, to include the provision of bulks and in-process samples. The company should supply the Secretariat with details of the assay procedures agreed with the National Institute of Biological Standards and Control.

Remark to SEAR

2. the Sub-Committee would look more favourably on an application for a Clinical Trial Certificate, provided it was recognised that long term toxicity data would need need to be available by the PL stage.

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PL/0086/0100	RECOMMENDATION
Coy.	On the evidence before them the Sub-Committee recommended the grant of a Product Licence on condition that:
Hoechst UK Ltd	1. satisfactory information was provided on the heat-treatment process; this should include the identity and concentrations of added stabilising agents,
Product	2. clarification was given on the electrophoresis data before and after heating, with special reference to the thermal degradation products of Factor VIII and clear statements were given on the change in Factor VIII potency,
Factor VIII H.S	
Therapeutic Class	3. the Finished Product Specification was amended to include:-
Antihaemophilic	i) a test with suitable limits for sodium,
Active Constituent	ii) a clear statement of the acceptance/rejection criteria in the microzone electrophoresis test,
Factor UIII 250 IU, 500 IU, 1000 IU per vial	iii) an upper limit of Factor VIII activity of not more than 125% of the labelled amount.
	4. suitable comparative results between the Behringwerke assay for Factor VIII and the BP 1980 assay was provided, together with confirmation that the Behringwerke standard is calibrated in IU against the WHO International Standard,
	5. additional stability data were provided showing the results of tests for degradation products on storage,
	6. confirmation was given that the air in the vial is removed or replaced by sterile oxygen free nitrogen,
	7. an assurance was given that the Albumin would comply, if tested, with all the tests in the BP specification,
	8. biological evidence of the reproducibility of the inactivation process was provided,
	9. the Data Sheet and Product Particulars were amended to the satisfaction of the Secretariat, with particular reference to:
	i) inclusion of a statement that the material was heat-treated;
	ii) no claims were made that the transmission of hepatitis B and non-A non-B hepatitis had been excluded;
	iii) no reference to AIDS was included except as a warning that blood products may transmit the syndrome,

No. PL/0086/0100 Coy. Hoechst UK Ltd Product Factor VIII H.S Therapeutic Class Antihaemophilic Active Constituent Factor UIII 250 IU, 500 IU, 1000 IU per vial	10. the Batch Release procedure should apply, to include the provision of bulks and in-process samples. Remark Further studies on the effectiveness of the inactivation process should be undertaken.

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PL/0022/0056	RECOMMENDATION
Coy.	On the evidence before them the Sub-Committee recommended the grant of a Product Licence on condition that:
KabiVitrim Ltd	1. satisfactory information was provided on the source of the plasma used,
Product	2. the indication was limited to replacement therapy for congenital agammaglobulinaemia and hypogammaglobulinaemia in patients who were unable to tolerate intramuscular administration,
Gammonativ	
Therapeutic Class	3. the finished product specification contained tests with suitable limits for:
Gammaglobulin	i) HB_s Ag.;
Active Constituent	ii) IgG; this should be not less than 90% of the total immunoglobulin content;
Immunoglobulin G 2.5 gm, 5.0 gm	iii) pre-kallikrein activator,
	4. full details of all in-house methods of analysis were provided, together with sample chromatograms showing resolution of monomeric and polymeric IgG and absence of Ig fragments,
	5. further information was provided on the IgG subclasses present in this preparation,
	6. further information was provided to explain the increase in high molecular weight materials on storage,
	7. further information was provided on the antibody profile, including antibody to HB_s Ag.,
	8. the Batch Release procedure should apply, to include the provision of bulks and in-process samples.

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PL/0093/0046-47	RECOMMENDATION ON WRITTEN REPRESENTATION
Coy. Servier Laboratories Ltd	The Sub-Committee considered the additional data supplied by the Company and they agreed to recommend the grant of a Product Licence on condition that:
Product Tetavax	1. the Company included a satisfactory sterility test suitable for detecting fungal as well as aerobic and anaerobic bacterial contamination of the vaccine in the final containers,
Therapeutic Class Bacterial Vaccine	2. the integrity of the sterilising filter used for thiomersal solution was tested before and after use,
Active Constituent Purified Tetanus Toxoid	3. batches were not released unless the Lf content per human dose was less than 12 and the potency of the vaccine complied with the European Pharmacopoeia,
	4. the Data Sheet and Product Particulars were modified to the satisfaction of the secretariat,
	5. on-going stability data was provided to check the potency of the vaccine up to expiry date,
	6. the Batch Release procedure should apply, to include the provision of bulks and in-process samples.