NOT FOR PUBLICATION CSM/85/8th Meeting

COMMERCIAL IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

GRO-C

24/10/85.

Minutes of the meeting held on Thursday 19 and Friday 20 September 1985, in the 19th Floor Conference Suite, Market Towers.

Present

Professor Sir Abraham Goldberg (Chairman)
Professor A M Breckenridge*
Dr C M Castleden*
Professor J W Dundee
Professor P H Elworthy
Professor D G Grahame-Smith*
Professor M W Greaves
Dr J M Holt*
Professor D Hull*
Professor H S Jacobs*
Dr B L Pentecost
Professor M D Rawlins*
Dr J W G Smith*
Dr M B Ward+
Professor H K Weinbren

Dr A T B Moir*

Dr R Mann (Medical Assessor)
Dr J Purves (Pharmaceutical Assessor)
Mr J Grimshaw (Secretary)
Mr K L Fowler (Assistant Secretary)
Dr P N Adams
Mr A C Cartwright*
Miss R Coulson*
Mr J P Digings
Dr M Duncan*
Dr S Fawcett
Dr L K Fowler
Dr M Glen-Bott
Dr A Isaacs*
Dr W Jenkins*
Dr J A Nicholson*
Mr M Pinel*
Dr J Ritchie
Dr D I Slovick
Mr A Stewart+
Dr K Winship

Also Present

Dr G Burton
Mr C Davis
Mr N Hale
Dr D Jeffreys
Mr D Lye*
Mr J E Parnwell+
Dr H Pickles
Mrs P Scoular*

*Thursday Only
+Friday Only

1. APOLOGIES AND ANNOUNCEMENTS

1.1 The Chairman repeated his usual reminder that the papers and proceedings are confidential and should not be disclosed.

1.2 Apologies had been received from Professor Asscher, Professor Florence and Professor Vessey for both days, from Dr Ward for Thursday, and from Dr Castleden, Professor Grahame-Smith, Dr Holt, Professor Rawlins and Dr Smith for Friday.

1.3 The Chairman informed members that, along with other members of the Committee and the Secretariat, he had recently attended a meeting of the British Association for the Advancement of Science and a meeting of the Association of Anaesthetists of Great Britain and Northern Ireland, both of which had been successful.

1.4 The Chairman congratulated Professor Rawlins on being invited to give the Bradshaw Lecture on "Preventing Adverse Reactions to Drugs".

1.5 The Chiarman congratulated Dr G Jones on his recent election as Vice Chairman to the CPMP in Brussels.

1.6 At the end of business on Thursday, the Chairman proposed that the quorum should be reduced to six for the meeting on Friday only, and this proposal was agreed.

2. MINUTES OF THE MEETING HELD ON THURSDAY 25 AND FRIDAY 26 JULY 1985

2.1 Item 1.3 of the minutes was amended to state that Professor Lawson had attended to advise the Committee on the Report of the Adverse Reactions Working Party as well as the papers concerning efficacy requirements for products for minor conditions.

2.2 The last sentence of item 1.8.3 was amended to read as follows: "Mr Hale went on to say that if any member felt he was being slandered or libelled, he could bring it to the attention of the Secretariat who could take advice, without prejudice to the right of members to contact their own defence society or legal advisors".

2.3 Following these amendments, the Chairman signed the minutes as a true record of the meeting.

3. MATTERS ARISING FROM THE MINUTES

3.1 In reply to members' concerns regarding the possibility of personal liability following the legal action initiated by the Opren Action Group, Mr Hale said that the Department would ~~stand behind~~ any member who was personally subject to any action arising out of CSM business.

3.2 Sustained Release Theophylline Preparations (and the associated applications); members were informed that consideration of this paper, and the applications, had been deferred to the October meeting of the SEAR Sub-Committee.

3.3 Report for members on Organon's Hydrocortisone Sodium Succinate Injection (tabled paper 1); Mr Hale informed the Committee that the Licensing Authority intended to renew the emergency suspension of these HSSI licences, and wished to proceed with formal suspension of the licences. The Committee endorsed this course of action.

4. CONSIDERATION OF APPLICATIONS

The Committee considered the applications listed, and their advice is given in Annex A.

4.1 Ultravist : PL/0053/0173-F : Schering

Consideration of this application was deferred for SEAR to review renal toxicity.

4.2 Carteolol Hydrochloride Eye Drops 1% & 2% : PL/0030/0040-1 : Zyma (UK) Ltd

Consideration of this application was deferred for SEAR to obtain specialist ophthalmological opinion.

4.3 ICI 162, 846 Tablets (0.5, 1, 2.5, 5, 10 & 20mg) and Injection (1mg/ml) : CT/0029/0189 : ICI Plc

4.3.1 Professor Elworthy declared a specific interest and took no part in the consideration of this application.

4.3.2 It was agreed that the Secretariat should discuss with the Company the points raised by Professor McLean's letter regarding this product.

4.4 Wellferon Injection : PL/0003/0220-1 : Wellcome Foundation

Consideration of this application was deferred back to the SEAR Sub-Committee.

4.5 Roferon - A : PL/0031/0201-2 : Roche Products Ltd

Consideration of this application was deferred back to the SEAR Sub-Committee.

4.6 Konyne - HT : PL/0055/0108 : Miles Laboratories Ltd

Following consideration of this application, the Committee discussed the issue of the heat treatment of biological products. They were of the view that the Licensing Authority should encourage the wet-heat treatment of products such as Factor VIII, and should require companies to demonstrate the lack of clinical infectious sequelae from their products.

4.7 Dr Reckeweg R45 : PL/5071/0007 : Pharmazeutische Fabrik

Consideration of this application was deferred to enable it to be considered by the CPS Sub-Committee.

5. WRITTEN REPRESENTATIONS

5.1 The Committee considered written representations on the following products:

5.1.1 Apolar 0.1% Cream : PL/3895/0020 : Alinter Ltd.

5.1.2 Aminoven 5 and 12 :PL/0075/0046-7 : MCP Pharmaceuticals.

5.2 The Committee's advice and reasons for that advice are given in Annex B.

6. HEARINGS

6.1 The Committee held Hearings on the following products:

6.1.1 Tonocard : PL/0017/0106-8 : Astra Pharmaceuticals Ltd.

6.1.2 Merieux Human Albumin : PL/0093/0044 : Servier Laboratories Ltd.

6.1.3 Theophylline Infusion : PL/0116/0123-8 : Travenol Laboratories Ltd.

6.2 The Committee's advice and reasons for that advice are given in Annex C.

7. PIROXICAM - SERIOUS GASTRO-INTESTINAL ADVERSE REACTIONS: FURTHER INFORMATION

The Committee considered this paper and endorsed the recommendation of the SEAR Sub-Committee that no regulatory action was required at this time. The situation would be reviewed, and the toxicity of piroxicam and of other non-steroidal anti-inflammatory agents would be the subject of another paper in the near future.

8. IMIDAZOLE ANTIFUNGAL PREPARATIONS

8.1 Professor Grahame-Smith declared a specific interest and took no part in the consideration of this paper.

8.2 Professor Rawlins declared a specific interest. The Chairman ruled that, in view of his relevant knowledge, he should communicate to the Committee on matters of fact but should not vote.

8.3 The Committee considered the paper, along with tabled paper 2 (a letter from Dr Sullivan), and noted the recommendations of the SEAR Sub-Committee.

8.4 The Committee agreed the following:

8.4.1 With regard to whether or not the contraindications in pregnancy for Ketoconazole, as a classic teratogen, should be extended to cover topical as well as oral preparations, it was agreed that regulation should be deferred pending the results of Professor Rawlins' study of the effects of Ketoconazole in the inflamed vagina. The Committee noted that Janssen had given an undertaking that the pessary would not be marketed until the study was completed.

8.4.2 The hazard associated with tioconazole nail solution 28% should be considered separately.

8.4.3 As the individual drug data on the other imidazoles are suggestive of, but do not prove, a risk in human pregnancy, no other action should be taken to vary the current licences at this time.

8.4.4 The pregnancy risk of imidazoles as a class would remain under review and receive specific attention if further applications are received for drugs of this class. Further licence applicants should be asked to address the possible hazard in late pregnancy.

8.4.5 The companies who are asked to submit data for this review should be informed of the Committee's recommendations.

9. TROSYL NAIL SOLUTION 28% : PL/0057/0236 : PFIZER LTD

On the evidence before them, the Committee had reason to think that, on grounds relating to safety, they would be unable to advise the grant of a product licence for this preparation, and advised the Secretary to notify the applicant in a second Section 21(1) letter.

The Committee provisionally concluded that:

9.1 On considering the animal data relating to pregnancy, the Committee were of the view that the product, in view of its high concentration, the possibilities of absorbtion, and the long treatment period, should be contraindicated in pregnancy.

9.2 The Committee specifically require:

9.2.1 Information on absorption into the blood of Trosyl Nail Solution applied to the nails.

9.2.2 An explanation of the significance of the animal data suggesting toxicity in pregnancy and the perinatal period.

10. CSM UPDATES - FOR INFORMATION

The Committee noted this paper, which listed articles for future publication.

11. CSM UPDATES - ARTICLES FOR APPROVAL

11.1 Chronic Ventricular Tachycardia : Adverse Drug Reactions

The Committee considered this article and approved it for publication subject to certain amendments. It was agreed that Tocainide should not be referred to without clearance from the Department's legal advisors.

11.2 Adverse Reactions to Antidepressants

The Committee considered this article, together with tabled paper 3 (an amended table), and approved it for publication subject to certain amendments.

12. GUIDELINES FOR THE HANDLING AND RECONSTITUTION OF CYTOTOXIC DRUGS

The Committee considered this paper and advised that similar guidelines should be applied to new product licence applications.

13. DI (2-ETHYLHEXYL) PHTHALATE (DEHP)

The Committee considered this paper and endorsed the recommendations of the SEAR Sub-Committee as follows:

13.1 A product licence can now be granted for Travamulsion 10% and 20% (PL/0116/0109-10 : Travenol).

13.2 No further action is needed on the subject of phthalate stripping from PVC giving sets.

14. TRAVAMULSION 10% AND 20% (PL/0116/0109-10 : TRAVENOL)

14.1 This application had been deferred by CSM in July, for consideration in the light of the previous paper.

14.2 The Committee endorsed the recommendation of the SEAR Sub-Committee that product licences should be granted.

14.3 Remark to the company : when phthalate giving sets become available, the company should recommend their use with the product.

15. LEGAL STATUS OF TOPICAL HYDROCORTISONE (tabled paper)

The Committee considered this paper and endorsed the recommendations of the SEAR Sub-Committee, with some amendments, as follows:

15.1 Hydrocortisone/Hydrocortisone Acetate only, at concentrations up to 1% in simple creams or ointments should be available for sale -(P).

15.2 The LA should have discretion regarding other bases or vehicles.

15.3 The indications should be: IRRITANT DERMATITIS, allergic dermatitis and insect bite reactions.

These indications may appear on advertising and labelling as agreed between the DHSS and PAGB but the term "Eczema" should not be used; "rash" and "dermatitis" would need qualification.

15.4 The contraindications should be: use on the eyes/face, ano-genital region, and on broken or infected skin such as cold sores or athletes foot. These contraindications may appear on advertising as in 3 above.

15.5 Children under age 10 years should not use the product except under medical supervision.

15.6 Dosage may be a thin application over a small area once or twice a day for a maximum of a week. If the condition is not improved, medical attention should be sought.

15.7 The pack size must be 10 or 15gms.

15.8 Advertising should be controlled by the DHSS assisted by the PAGB. Each pack should be labelled clearly "Contains Hydrocortisone".

15.9 Package inserts should be simple and factual, contain no promotional material, and restrict their content to the indications, warnings, precautions and such directly relevant material.

16. LEGAL STATUS OF FLUOCORTIN BUTYL 0.75% (NOVODERM CREAM) - PL/0053/0134 (tabled paper)

The Committee considered this paper and endorsed the recommendation of the SEAR Sub-Committee that there was insufficient evidence of safety and efficacy in clinical use for a change of legal status from POM to P.

17. SECRETARY/MEDICAL ASSESSOR'S ORAL REPORT

Dr Mann reported on the recent Leeds Castle conference on orphan drugs, and the provisions already existing in the EEC directives for marketing authorisations in respect of drugs for rare therapeutic indications.

18. DATE AND TIME OF NEXT MEETING

Thursday 24 October 1985 at 10.30 am.

No:

PL 0055/0108

Coy:

Miles Laboratories Ltd

Product:

Konyne-HT

Therapeutic Class:

Blood Product

Active Constituent:

Factor IX
Factors II, VII & X

MAIN COMMITTEE

ADVICE 19/20.9.85

On the evidence before them the Committee had reason to think that on grounds relating to safety, quality and efficacy they would be unable to advise the grant of a Product Licence for this preparation and directed the Secretary to notify the applicant in accordance with Section 21(1) of the Act.

The Committee provisionally concluded that:

1. Inadequate information had been provided on the manufacture and control of the sterile water for injection vials.

2. Inadequate information had been provided on the fractionation and control procedures.

3. Information should be provided on the standards used in finished product testing.

4. Inadequate evidence had been provided of virus inactivation.

5. Insufficient evidence had been provided of the clinical safety and efficacy of the product or of the product on which it is based.

Remarks

1. The Company should be asked what plans they have for the screening of donors against infectious agents, including HTLV-III.

2. In the event of a product licence being granted, the batch release procedure should apply, to include the provision of bulk and in-process samples.