GA

CSM/Mins/83/3

COMMERCIAL IN CONFIDENCE

CSM/83/3rd Meeting

COMMITTEE ON SAFETY OF MEDICINES

Minutes of the meeting held on Thursday 24 March 1983

Present

Professor A Goldberg (Chairman)
Professor M D Rawlins
Professor W I Cranston
Professor H K Weinbren
Professor P H Elworthy
Professor R H Girdwood
Professor M P Vessey
Professor J Dundee
Professor A T Florence
Dr M Richards
Mr W Darling
Dr J M Holt
Professor B M Hibbard
Professor F A Jenner
Professor A E A Read
Dr J Smith
Professor A Breckenridge

Also Present

Mr N M Hale
Dr J P Griffin
Mr P Allen
Mr G Berry

Committee Secretariat

Dr G Jones (Medical Assessor)
Dr J Calderwood (Pharm. Assessor)
Miss Z Spencer (Secretary)
Mr J Griffiths
Mr T Kirkley
Dr K Fowler
Dr A Nath
Dr S Grieve
Dr C Speirs
Dr G Diggle
Dr H Pickles
Dr A Nicholson
Dr M Duncan
Miss H Mallett
Dr K Winship
Mr A C Cartwright
Dr J C P Weber
Dr R D Mann
Dr M Glen-Bott
Dr B Matthews
Dr J Purves
Mr H Morgan
Mr M Noterman

GRO-C

21 April 1983

1. APOLOGIES AND ANNOUNCEMENTS

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

1.2. Apologies had been received from Professor Grahame-Smith and Professor Hull.

1.3. The Chairman welcomed Professor Florence who was attending this meeting of the Committee particularly for the hearing on Kalinorm.

1.4. The Chairman introduced Professor Alisdair Breckenridge. Professor Breckenridge had been appointed a member of the Committee in the place of the late Professor James Crooks and was attending his first meeting.

1.5. The Chairman announced that a meeting of the Working Party on Adverse Reactions had taken place on 10 March. In the absence of Professor Grahame-Smith, he was acting as Chairman of the Working Party. At the meeting aspects of the present yellow card system, and the Prestel system proposal by Professor Grob were discussed. Following the meeting Professor Goldberg and Ms Spencer had visited the computer facility at Reading.

1.6 Dr Griffin informed members of the death of Dr Dennis Cahal, and paid tribute to Dr Cahal's life and work.

2. MINUTES OF THE MEETING HELD ON 24 FEBRUARY 1983

The Chairman signed the minutes as a true record of the meeting after the following amendment had been made:

OXMETIDINE TABLETS: CT/0002/0105: SMITH KLINE AND FRENCH

The Committee's provisional conclusion was amended to read:

"They would require further information on the effects of the drug on the stomach of the rat with particular reference to the development of hyperplasia or hyperkeratosis since these changes had not been observed in other marketed H2 receptor blocking agents".

3. MATTERS ARISING FROM THE MINUTES

3.1. CSM/ABPI Dinner 24 February 1983

The Chairman informed members that the meeting and dinner had been both a pleasant and useful occasion.

4. PAPER 1 - NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

4.1. The Committee considered this paper and advised that:

4.1.1. Guidelines on pharmacokinetics:

Particular attention should be paid to:

a. identification of the major metabolic pathways in animals used in the chronic toxicity studies and in man,

b. the determination of plasma levels in animals and in man.

These studies should attempt to compare repeat dose plasma levels in toxicity studies and clinical studies.

4.1.2. Guidelines on carcinogenicity:

a. The guidelines should emphasise that there should be good animal husbandry throughout the studies,

b. in studies using drugs of high toxicity, the guidelines should be strictly adhered to, with the top dose animals showing minimal toxic effect.

4.1.3. In assessing carcinogenicity studies particular attention should be paid to the survival of animals in the control and treatment groups. The results of the carcinogenicity test would not normally be regarded as negative unless there was a 50% or better survival of the control animals for 18 months from the start of the dosing in the mouse and 2 years in the rat and with sufficient numbers of surviving treated animals for reasonable statistical evaluation."

4.2. The Committee did not consider that any alterations to the pharmacokinetic or carcinogenicity guidelines were necessary, but did consider that they should be more strictly enforced.

5. PAPER 2 - STARCH BLOCKERS

5.1. The Committee considered this paper and advised that:

5.1.1. Starch blockers were being used for a recognised medicinal indication, namely obesity.

5.1.2. There was no evidence that any of the products were efficacious.

5.1.3. There was some evidence of toxicity in animals affecting the pancreas and the microvilli of the small intestine; there was a theoretical cause for concern about the use of these products in man because of these effects. In particular, changes in the pancreas might be indicative of neoplastic potential.

5.1.4. There was a theoretical concern that the attachment of lectins to the gut mucosa might result in neoplastic change.

5.1.5. There was no evidence of serious adverse reactions in man although no attempt to look for such reactions had been made.

5.2. The Committee recommended that Ministers should consider this advice and take whatever action they considered appropriate.

6. PAPER 3 - ZOMAX

The Committee considered this paper and agreed that no action should be taken against the product licence. Dr Weber reported that the company were aware of eight deaths and approximately five hundred allergic reactions in the United States. The Committee were informed that the Company were planning to re-launch the product with amended prescribing advice. A variation application would be submitted and would be seen by the Committee.

7. PAPER 4 - IBUPROFEN (NUROFEN)

7.1. The Committee considered this paper and confirmed its provisional advice that the legal status of Ibuprofen should change from POM to P.

7.2. The Committee considered that certain aspects of the promotional literature should be amended, in particular:

7.2.1. the reference to comparative efficacy in relation to aspirin and paracetamol,

7.2.2. the statement on the effect on the stomach.

7.3. The Committee confirmed that at the appropriate time they would wish to see an item in Current Problems on the change in legal status of Ibuprofen.

8. PAPER 5 - CONGENITAL MALFORMATIONS STUDY - PHASE 3 - NEURAL TUBE DEFECTS

8.1. The Committee considered the further paper and the written comments from Professor Vessey and Professor Hibbard.

8.2. The Committee advised that:

8.2.1. the paper should not be published because of concern regarding the validity of the findings and the likelihood that its publication would prejudice the prospective MRC trial on the use of folates to prevent neural tube defects,

8.2.2. there should be further consideration of whether it was justifiable to use CSM resources in a new study on congenital malformations. Professor Vessey and Professor Hibbard should be consulted regarding the type of defect that might be investigated and the precise design of any such study,

8.2.3. the Committee deferred reaching a decision on whether any further study should be undertaken and would reconsider the matter at its next meeting. Before reaching a decision the Committee would require to see a formal detailed protocol of any such study.

9. PAPER 6 - CURRENT PROBLEMS

The Committee considered and approved the drafts of paragraphs for inclusion in future issues of Current Problems, subject to a number, of draft amendments.

10. TABLED PAPER 2 - SUDAFED LINCTUS: PL/0003/0163: THE WELLCOME FOUNDATION LIMITED

The Committee considered this paper and decided that it wished to have a full hearing on the warnings regarding asthma, drowsiness and alcohol.

11. CONSIDERATION OF APPLICATIONS

11.1. The Committee considered the applications listed and their advice is contained in Annex A to these minutes.

11.2. Tildiem Tablets: PL/4969/0005: Lorex

Professor Weinbren declared an interest.

11.3. Rapifen Injection: PL/0242/0021: Janssen Pharmaceuticals Limited

Professor Rawlins declared an interest.

11.4. Oncovin Solution Hyporets: PL/0006/0176: Lilly Industries Limited

Professor Elworthy declared an interest.

11.5. Profilate: PL/4029/0001: Alpha Therapeutic

This application was withdrawn.

12. WRITTEN REPRESENTATION - FENTICONAZOLE CREAM: CT/4595/0001: RECORDATI SpA

The Committee considered this application and their advice is given in Annex B to these minutes.

13. HEARING 1 - KALINORM MODIFIED RELEASE TABLETS: PL/4338/0002: A/S ALFRED BENZON

The Committee considered this application. The Committee's advice and the reasons for that advice are given at Annex C to these minutes.

14. HEARING 2 - PENKIT: PL/4534/0001: LABORATOIRE DES STALLERGENES

The Committee considered this application. The Committee's advice and the reasons for that advice are given at Annex D to these minutes.

15. MINUTES OF THE SEAR MEETING HELD ON FRIDAY 7 FEBRUARY 1963

The Committee noted these minutes which were for information.

16. SECRETARY/MEDICAL ASSESSORS ORAL REPORT

None.

17. ANY OTHER BUSINESS

None.

18. DATE AND TIME OF NEXT MEETING 21 APRIL 1983 AT 10.30 AM

No.

PL 4447/0004

Cov.

Alpha Therapeutic (UK) Ltd

Product

Antihaemophilic Factor (Human) Wet-Paste (Bulk Cryoprecipitate)

Therapeutic Class

Blood Product

Active Constituent

Human Factor VIII

24.3.83

Main Committee

Advice

On the evidence before them the Committee had reason to think that on grounds relating to safety and quality 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. the bulk cryoprecipitate should be prepared by Alpha Therapeutic only from Source Plasma (Human) derived from their own licensed plasmapheresis centres,

2. evidence should be provided to show that the cryoprecipitate is at least equivalent in quality to that used for the manufacture of Alpha Therapeutic's US licensed Factor VIII,

3. inadequate information was presented on the control of the material during transport to the UK,

4. an undertaking should be given that donor lists should be available to the manufacturer of the finished dosage form,

5. in the event of a licence being granted for this product, the batch release procedure should apply, to include the provision of protocols and samples of bulks, as required,

6. there were inadequate details on the manufacturing process.

Remarks

1. The Licensing Authority is asked to consider the legal implications of licensing this bulk blood product as an ingredient rather than as a finished product, especially in view of the great difficulties foreseen for the manufacturer of the finished dosage form in exercising full control going back to the source material.

2. The Committee advised that special attention be given to the inspection of the Company's premises in the USA.

3. The Committee noted that no evidence of efficacy was provided as the product was intended only as an ingredient.

No.

CT 3070/0006

Coy.

Speywood Laboratories Ltd

Product

Mono-VIII C

Therapeutic Class

Blood Product

Active Constituent

Human Factor VIII

24.3.83

Main Committee

Advice

On the evidence before them the Committee had reason to think that on grounds relating to safety and quality they would be unable to advise the grant of a clinical trial certificate 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:

Bulk Cryoprecipitate

1. the bulk cryoprecipitate should be prepared by Alpha Therapeutics only from Source Plasma (Human) derived from their own licensed plasmapheresis centres,

2. evidence should be provided to show that the cryoprecipitate is at least equivalent in quality to that used for the manufacture of Alpha Therapeutic's US licensed Factor VIII,

3. inadequate information was presented on the control of the cryoprecipitate during transport to the UK,

4. inadequate information had been provided on the control of the quality of the cryoprecipitate on arrival in this country and throughout its transit in the UK,

5. donor lists should be available to Speywood Laboratories Ltd as manufacturer of the finished dosage form,

6. inadequate details of the manufacturing process of the bulk cryoprecipitate were supplied,

Mono VIII : C

7. full details should be supplied on the manufacturing and control methods of the product. This should include definitive information on in-process sterilisation methods and microbiological control,

8. reverse osmosis water should not be used in the preparation of this product,

9. bubble-point testing should be carried out on the sterilising filter before and after filtration,

No.

CT 3070/0006

Coy.

Speywood Laboratories Ltd

Product

Mono-VIII C

Therapeutic Class

Blood Product

Active Constituent

Human Factor VIII

10. the FPS should include tests and limits for Loss on Drying, Isoagglutinins and Pre Kallikrein Activator,

11. full information should be supplied on the manufacture and quality control of the 5 ml diluent supplied with the injection,

12. in the event of a Clinical Trial Certificate being issued the study should be limited to 10 patients and to no more than one bleeding episode in each patient.

Remarks

1. By Product Licence Stage:

1.1 evidence should be provided to show that the manufacturing process yields a consistent product,

1.2 evidence should be provided concerning the long term toxicity of the product and its possible contaminants,

1.3 evidence of clinical pharmacology of the product would be required,

2. In the event of a clinical trial certificate being issued for this product, the batch release procedure should apply, to include the provision of protocols and samples of bulks, as required.