GRO-C

23/2/84

CSM/84/1st Meeting

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

Minutes of the meeting held on 26th and 27th January 1984 at Market Towers 1 Nine Elms Lane London SW8.

**Present**

Professor Sir Abraham Goldberg (Chairman)
Professor A W Asscher x
Professor A M Breckenridge x
Dr C M Castleden x
Mr M W Darling
Professor P H Elworthy
Professor A T Florence
Professor D G Grahame-Smith x
Dr J M Holt
Professor D Hull x
Dr B L Pentecost +
Professor M D Rawlins x
Dr J W G Smith
Professor M P Vessey x
Dr D M B Ward
Professor H K Weinbren

( x Thursday only)
( + Friday only)

Dr G Jones (Medical Assessor)
Dr J Calderwood (Pharmaceutical Assessor)
Mr J Grimshaw (Secretary)
Mr A C Cartwright
Miss R Coulson
Dr M Duncan
Dr S Fawcett
Dr R Fowler
Dr M Glen Bott
Dr S Grieve
Mr J Griffiths
Mr T Kirkley
Mr H Morgan
Dr J Nicholson
Dr H Pickles
Dr C Speirs
Dr C Twomey
Dr P Weber
Dr R A Winship
Dr S Wood

Also Present

Mr N M Hale
Dr J P Griffin
Mr P Allen
Mr C Davies
Mrs M Dow
Mr M Smith

1. APOLOGIES AND ANNOUNCEMENTS

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 Dundee, Professor Greaves and Professor Jacobs for both days, Dr Pentecost for Thursday and from Professor Asscher, Professor Breckenridge, Dr Castleden, Professor Grahame-Smith, Professor Hull, Professor Rawlins and Professor Vessey for Friday.

1.3 The Chairman introduced and welcomed Professor Asscher, Dr Pentecost, Dr Castleden and Dr Ward who were attending their first meeting of the Committee.

1.4. The Committee agreed with the Chairman's suggestion that the quorum should be reduced to five for this meeting.

2. MINUTES OF THE MEETING HELD ON THE 15 DECEMBER 1983

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

paragraph 10:1 first line was amended to read: "the Committee considered this paper and agreed to waive the condition regarding microscopic confirmation of the macroscopic diagnosis of the liver changes".

3. MATTERS ARISING FROM THE MINUTES

3.1 Flosint Tablets: PL 3433/0034: Farmitalia Carlo Erba

The Chairman informed members that the information requested by the Committee at the December meeting had been suppliedby the Company and that a paper would be before the Committee at the February meeting.

3.2 Oral Contraceptives and Cancer

Professor Vessey informed the Committee of a further proposed epidemiological study by himself and Professor Pike concerning breast cancer and oral contraceptives. The Committee confirmed that they remained seriously concerned about the possible carcinogenic effects, especially on the breast, of oral contraceptive use and that they welcomed further work on this topic. The Committee asked that their views be communicated to Dr Bodmer, the ~~Secretary~~ Director of the ICRF. ~~Cronte Committee.~~

4. CONSIDERATION OF APPLICATIONS

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

5. PAPER FABROL (ACETYLCYSTEINE) ADVERSE REACTIONS

5.1 The Committee considered this paper and the recommendation of the SEAR Sub-Committee.

5.2 The Committee endorsed the recommendation of the Sub-Committee that:

5.2.1 the companies should be asked informally to include warnings in their data sheets for Fabrol and Fluimucil to the effect that Bronchospasm and anaphylactoid reaction have occured in patients taking acetylcysteine in the oral form.

5.2.2 an entry should be included in the next edition of Current Problems warning doctors of these possible reactions and requesting yellow card reports of all adverse reactions associated with acetylcysteine whenever it is used in the treatment of respiratory disorders.

6. PAPER MATERNAL DRUG HISTORIES AND CENTRAL NERVOUS SYSTEM ANOMALIES

6.1 The Committee considered this paper. Professor Vessey commented that various amendments had been proposed previously and had been incorporated into a later version of the paper. The Committee noted the comments of Professor Elstein and that he was in favour of the paper's publication. The Committee decided that they had no objection to the paper being submitted for publication by the authors.

7. PAPER BENOXAPROFEN (OPREN) : CT 0006/0087 : Eli Lilly Ltd

The Committee noted this paper.

8. PAPER SODIUM HYMECROMONE INJECTION :CT 3759/0009: Lipha Pharmaceuticals Ltd : Suspension of Clinical Trial Certificate

8.1 The Committee considered this paper and provisionally concluded that they might have to advise the Licensing Authority that the above-named clinical trial certificate should be suspended for a period of 12 months on grounds relating to safety. The reason for this was:
the specifications and standards to which any substancies or articles (to which the certificate relates)are manufactured can no longer be regarded as satisfactory.

8.2 The Committee decided that they would determine their advice to the Licensing Authority at their meeting in April 1984.

9. PAPER ALTHESIN: PL 0004/0189 : Suspension by the Italian Drug Regulatory Authority.

The Committee noted this paper.

10. TABLED PAPER WORKING PARTY ON ADVERSE REACTIONS: Phase 2

The Committee noted this paper.

11. TABLED PAPER ADVERSE REACTION GROUP OF THE SUB-COMMITTEE

The Committee endorsed and welcomed the establishment of the Group

12. WRITTEN REPRESENTATIONS

12.1 The Committee considered the following written representations. Their advice and reasons for their advice are given in Annexes B to K of these minutes:

Tildiem Tablets: PL 4969/0005 : Lorex Pharmaceuticals Ltd
Noroxin Tablets: PL 0025/0182-4 : Merck, Sharp and Dohme Ltd
Anti-haemophilic Factor (Human) Wet Paste (Bulk Cryoprecipitate): PL 4447/0004: Alpha Therapeutic Corporation
Biorphen Liquid : PL 4532/0002 : Bio Medical Services Ltd
Aldoretic/Aldoretic Forte: PL 0025/0179-80: Merck, Sharp and Dohme Ltd
Verapamil Tablets: PL 4569/0018-19: Generics (UK) Ltd
Bilimiro Tablets : PL 0493/0071 : E Merck Ltd
Dopamine Hydrochloride Sterile Powder : PL 3265/0063-65: International Medication Systems Ltd

Tylenol with Codeine Elixir:PL/0076/0010:Ortho-Cilag Pharmaceuticals Ltd

12.2 Tylenol with Codeine Tablets:PL/0076/0100-0103 : Ortho-Cilag Pharmaceuticals Ltd

The Committee deferred consideration of this written representation until the February meeting.

13. HEARINGS

13.1. The Committee held hearings on the following products:

Flenac Tablets: PL/0044/0060: Reckitt and Colman
Methrazone Capsules: PL/0015/0071R: Boehringer Ingelheim Ltd

13.2 The Committee's advice and reasons for that advice are given in Annexes L and M to these Minutes.

14. SECRETARY- MEDICAL ASSESSORS ORAL REPORT

14.1 Osmosin : PL/0025/0148: Merck, Sharp and Dohme Ltd
Dr Jones informed members that the Company now had no plans to remarket this product and had surrendered the product licence.

14.2. Hearings on Products containing Phenylbutazone and Oxyphenbutazone scheduled for February meeting.

Dr Jones informed the Committee that these hearings would not now take place as the Company concerned, Ciba-Geigy, had submitted written representations.

15. ANY OTHER BUSINESS

None

16. DATE AND TIME OF NEXT MEETING

Thursday 23 February 1984 at 10.30 am.

COMMERCIAL IN CONFIDENCE

CSM/84/1st Meeting

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

PL/4447/0004

Antihaemophilic Factor (Human) Wet Paste (Bulk Cryoprecipitate)

Alpha Therapeutic Corporation

WRITTEN REPRESENTATION 3

Medical Assessor: Dr L K Fowler

Pharmaceutical Assessor: Mr J Betts

## 1. BACKGROUND

1.1 An application for a Product Licence for this product was received on 7 December 1982.

1.2 The application was considered by the Committee at their meeting in March 1983. The Committee had had reason to think that on grounds relating to safety and quality they would be unable to advise that the licence applied for should be granted.

1.3 The Committee had 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.

1.4 The Company was informed of this in a letter sent on 12 April 1983 in accordance with Section 21(1) of the Medicines Act 1968 and had exercised its right to submit written representations to the Committee in support of its application.

## 2. ADDITIONAL DATA

The Company had submitted one volume of data in reply to the Section 21(1) letter.

3. FINDINGS

3.1 The Committee noted that the Company were unable to confirm that the bulk cryoprecipitate would be prepared by Alpha Therapeutic only from source plasma (Human) derived from their own licensed plasmapheresis centres and the Company's arguments for an alternative arrangement were not accepted. The Committee were therefore not reassured on point 1 of the Section 21(1) letter.

3.2 The Committee considered that satisfactory evidence had not been 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. The Committee were therefore not reassured on point 2 of the Section 21(1) letter.

3.3 The Committee considered that the information presented on the control of the material during transport to the UK was inadequate. The Committee were therefore not reassured on point 3 of the Section 21(1) letter.

3.4 The Committee noted that the Company had provided a satisfactory undertaking to supply donor lists to the manufacturer of any finished dosage form and they were therefore reassured on point 4 of the Section 21(1) letter.

3.5 The Committee did not accept the Company's argument that the batch release procedure should not apply and therefore they were not reassured on point 5 of the Section 21(1) letter. The Committee still considered that in the event of a licence being granted for this product, the batch release procedure, including the provision of protocols and samples of bulks as required, should apply.

3.6 The Committee considered that satisfactory details of the manufacturing process had been provided and they were reassured on point 6 of the Section 21(1) letter.

4. ADVICE

The Committee were unable to advise the Licensing Authority that a licence be granted on grounds of safety and quality.

5. REASONS FOR ADVICE

The Committee were still concerned about the safety and quality of this product as indicated in points 3.1, 3.2, 3.3 and 3.5 above.