COMMERCIAL IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

Minutes of the meeting held on Thursday 29 and Friday 30 May 1986, in the 19th floor Conference Suite, Market Towers.

Present

Professor Sir Abraham Goldberg (Chairman)
Professor A W Asscher *
Professor A M Breckenridge *
Dr C M Castleden *
Mr W M Darling
Professor J W Dundee
Professor F 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 *
Professor M P Vessey *
Dr D M B Ward
Professor H K Weinbren

Guest Members

Professor M Elstein *
Dr J L Mann +

* Thursday only
\+ Friday only

Dr A J Isaacs (Medical Assessor)
Dr J Purves (Pharmaceutical Assessor)
Miss A Simkins (Secretary)
Mr K L Fowler (Assistant Secretary)
Dr P N Adams *
Miss R Coulson *
Mr J Digings
Dr L K Fowler
Dr A M Glen-Bott *
Dr W J Jenkins *
Dr G Jones *
Dr R Mann
Dr B Matthews *
Dr A Nath *
Dr J A Nicholson *
Miss S Norton +
Mr M Pinel
Dr J Ritchie
Dr F Rotblat
Dr D I Slovick *
Mr J Turner *
Dr K Winship *
Dr S Wood

Also Present

Mr D Dunleavy
Mr J Griffiths *
Mr D Hagger *
Mr N Hale
Miss S Hanson *
Dr L Hill *
Dr D Jefferys *
Mr D Lye *
Dr A T B Moir *
Mr C Seabrooke *

1. APOLOGIES AND ANNOUNCEMENTS

1.1 The Chairman reminded members that the papers and proceedings are confidential and should not be disclosed.

1.2 Apologies for absence were received from Professor Florence for both days, and from Professor Asscher, Professor Breckenridge, Dr Castleden, Professor Grahame-Smith, Dr Holt, Professor Hull, Dr Smith and Professor Vessey for Friday.

1.3 The Chairman informed members that Dr Lisa Hill would be attending on Thursday to introduce the paper on her Congenital Malformations Study. Professor Elstein of the SEAR Sub-Committee would also be attending as a guest member on Thursday to advise the Committee with regard to the written representation for Yutopar Capsules, and Dr J L Mann of the Department of Community Medicine and General Practice, Radcliffe Infirmary, would be attending as a guest member on Friday to advise the Committee with regard to the Hearing for MaxEPA Capsules and Liquid.

1.4 The Chairman reported that he had signed an affidavit, at the request of Glaxo, affirming the importance of confidentiality for voluntary reports of adverse reactions.

2. MINUTES OF THE MEETING HELD ON WEDNESDAY 30 APRIL 1986

The minutes were agreed and signed by the Chairman as a true record of the meeting, subject to the amendments listed on tabled paper 1, and a typing correction.

3. MATTERS ARISING FROM THE MINUTES

3.1 Item 4.3: Prazosin Hydrochloride Tablets.

Dr Isaacs reported that members of the Secretariat had held a meeting with representatives of Generics (UK) as a result of which the Company had proposed withdrawing the 5 mg tablet and submitting further data to show the bioequivalence of the 2 mg tablet with 2 mg of Hypovase. The applications would therefore be deferred, probably until the September meeting of CSM, when the new evidence could be considered.

3.2 Item 5.1.2: Cardene.

Dr Isaacs reported that Syntex Pharmaceuticals had agreed the data sheet amendments regarding the starting dose and the angina warning.

4. APPLICATIONS

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

4.2 Cytotec 200 and 400 mcg tablets: PL 0020/0115-9: G D Searle.

4.2.1 In connection with this application the Committee noted tabled paper 4 (revised data sheet and further information from the Company).

4.2.2 After considerable discussion a vote was taken on whether to advise the grant of licences on the conditions recommended by the SEAR and CPS Sub-Committees. This course of action was rejected by 11 votes to 6. A second vote on whether to advise the grant of licences on the additional condition that the data sheet should carry

a stronger warning restricting treatment to eight weeks, together with a rationale for this treatment, was lost by 9 votes to 8.

4.2.3 Professor Grahame-Smith, Dr Smith and Professor Asscher wished it to be recorded in the minutes that they objected strongly to the grant of a licence being withheld on the grounds that the product might be misused.

4.2.4 It was agreed that the Section 21(1) letter should be approved by the Chairman before posting.

5. WRITTEN REPRESENTATIONS

5.1 The Committee considered a written representation on the following product:

Yutopar SR 40 mg Capsules: Pl 0512/0069: Duphar Laboratories

The Chairman introduced and welcomed Professor Elstein of the SEAR Sub-Committee, who was attending to advise the Committee with regard to this written representation.

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 Pinacidil: CTC 0043/0074: Leo Laboratories

6.1.2 MaxEPA Capsules and Liquid: PL 1932/0002-3: Seven Seas Health Care Ltd

6.1.3 Securon SR: PL 0169/0007: Knoll Ltd

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

7. CONGENITAL MALFORMATIONS STUDY

7.1 The Chairman introduced and welcomed Dr Lisa Hill who introduced the paper, together with a more detailed analysis of the figures in relation to beclomethasone, betamethasone and sulphonamides/trimethoprim, as suggested by the SEAR Sub-Committee.

7.2 The Committee received the paper with great interest, and congratulated Dr Hill and her colleagues on their work.

7.3 Among other points, Professor Vessey drew attention to the increased risk of oral clefts following oral contraceptive use. He said that he would send Dr Hill some further comments in writing.

7.4 Professor Breckenridge asked Dr Hill to provide a breakdown of other drug therapy, including anticonvulsants, taken by patients on oral contraceptives and Dr Hill agreed that this information could be provided.

7.5 Professor Hull noted that there was no evident protective effect from the administration of folate and vitamins, and asked whether these might have been available from other sources. Dr Hill said that this could

7.6 The Committee endorsed the recommendation of the SEAR Sub-Committee that ARGOS should consider the ways in which the relationship between congenital malformations and drug therapy might be further investigated.

8. REYE'S SYNDROME AND ASPIRIN

8.1 Mr Hagger introduced the paper and reported on recent developments. After consideration of the papers provided by the Aspirin Foundation, the Committee confirmed the conclusion reached at the March meeting that there is a need for action to reduce the use of aspirin by children.

8.2 The Committee discussed possible label warnings and advised that labels of all oral preparations containing aspirin should display the warning: "Do not give to children under 12 unless your doctor tells you to".

8.3 The Committee welcomed the positive and helpful response by the pharmaceutical industry to their provisional recommendations, and endorsed the Licensing Authority's general approach on publicity. The Committee considered that the 'Dear Doctor' letter should be posted one day earlier than proposed, to give the professions advance warning. It was also suggested that prior discussions should be held with the RCGP, GMSC and PSGB.

8.4 Mr Darling suggested that a letter should appear in the Pharmaceutical Journal asking pharmacists to deal personally with all requests for paediatric aspirin preparations, and offered to assist with this.

8.5 The Committee considered the text of the proposed 'Dear Doctor' letter and agreed it, subject to a number of amendments and the inclusion of an additional paragraph informing doctors of the CMO's press conference on 12 June and the subsequent publicity campaign. The letter should also reflect the Committee's view, after discussion, that paracetamol was an effective remedy for fever in children, but should not mention tepid sponging.

8.6 The Committee agreed to the proposal that the 'CSM Update' on Reye's Syndrome and Aspirin should be published on Saturday 14 June.

8.7 The Secretariat undertook to send members a copy of the briefing notes to be used by the CMO at the press conference.

8.8 The Committee considered that it might become necessary to reconsider the use of aspirin for children if new evidence on Reye's Syndrome became available. They considered it of fundamental importance that the British Reye's Syndrome surveillance scheme should be continued and wished their view to be brought to the attention of the PHLS and those responsible for funding it.

8.9 The Committee would be interested in observing whether a drop in aspirin consumption has an effect on the numbers of Reye's Syndrome cases reported, and hoped that clinicians would not use prior aspirin consumption as a diagnostic criterion.

9. CSM UPDATE: REYE'S SYNDROME AND ASPIRIN

The article was agreed for publication subject to a number of amendments.

10. OPREN

10.1 In connection with this paper, the Committee noted tabled paper 2 (comments from Professor Florence).

10.2 The Committee considered the paper, including the unpublished paper prepared in 1982 on ADRs to Opren. Other documents relating to Opren were available in the Committee room for inspection by members.

10.3 Dr Jenkins reviewed the current position. He reported that the majority of plaintiffs for whom details were known claimed to have suffered from onycholysis and/or photosensitivity, both of which reactions were well known at the time of licensing to be caused by Opren, and/or risk of cancer. There were apparently no claims so far in which the patient suffered the hepato-renal adverse effects causing death which led to the withdrawal of Opren.

10.4 Members discussed their recollections regarding the licensing and withdrawal of Opren.

10.5 It was suggested that a defence should be prepared against any possible accusation that the change in the Sub-Committee structure in January 1982 had been the result of inherent weaknesses in the previous structure.

10.6 Members expressed concern that Medicines Division was handling the considerable work involved in litigation within existing resources.

11. CSM UPDATE: WHAT LIES BEHIND THE PREGNANCY WARNINGS IN DATA SHEETS?

11.1 The Committee considered the paper, including tabled paper 5 (a revised draft of the article), and noted the recommendations of the SEAR Sub-Committee.

11.2 It was agreed that a further revision should be carried out in conjunction with Professor Elstein, incorporating the actual pregnancy warnings.

12. CSM UPDATE: DEVELOPMENT OF DRUG REGULATION - A GLOBAL VIEW

This paper was withdrawn from the agenda.

13. CSM UPDATES

13.1 The Committee noted the paper, listing 'CSM Updates' already published and those proposed for future publication.

13.2 It was agreed that the article on Reye's Syndrome should appear in mid-June, with the result that there would not be a 'CSM Update' in July. It was noted that the article on 'Drugs in Infectious Diseases' and an article by Professor Rawlins reviewing ADRs reported in 1985 would soon be ready for consideration by the Committee.

14. MANUFACTURE OF BLOOD PRODUCTS FROM PLASMA DERIVED FROM UNSCREENED DONORS

The Committee considered the paper, and endorsed the recommendations of the Biologicals Sub-Committee as follows:

14.1 All imported albumin preparations and the other products listed in this paper should be prepared from plasma individually tested for HBSAg and anti-HTLV-III. The Companies involved should be asked to apply for

variations to their Product Licences to cover this point, as soon as possible.

14.2 Details of the method of testing of HBSAg and HTLV-III antibody should be supplied.

14.3 All preparations not subject to the batch release procedure should be required to comply with it.

14.4 The attention of the Elstree and Edinburgh Fractionation Centres should be drawn to these recommendations.

15. RETIN-A ACNE TREATMENT: LOTION 0076/0037, GEL 0076/0050, CREAM 0076/0056

15.1 The Committee considered the paper, and endorsed the recommendation of the SEAR Sub-Committee that the Retin A product particulars should be amended to include the same warnings and precautions with regard to use in pregnancy and women of child-bearing potential as the current Roaccutane data sheet, set out at Annex D.

15.2 In the event of the Company not complying voluntarily with the recommendations, the Committee endorsed the Licensing Authority's proposal for compulsory variation, which was tabled.

16. GUIDELINES ON THE PRECLINICAL TESTING OF BIOLOGICAL PRODUCTS

The Committee considered the draft guidelines and noted the suggestions of the SEAR and Biologicals Sub-Committees. Members were invited to submit any further comments to Dr Fawcett. The Committee were informed that the final version of the paper would be brought back after consultation.

17. A PROPOSAL FOR THE USE OF INTERNATIONAL UNITS (IU) FOR THE EXPRESSION OF POTENCY IN CERTAIN ALLERGENIC EXTRACTS

The Committee considered the paper, and endorsed the recommendations of the Biologicals Sub-Committee as follows:

17.1 The potency of the final formulations of allergens should be expressed in International Units where calibrated international standards exist, if the allergen component is believed to be clinically important.

17.2 The potency and its method of measurement must be given on the label or the Data Sheet. Eg potency = 10,000 IU per ampoule by RAST inhibition.

17.3 For an interim period of possibly 5 years it is suggested that the potency of extracts should be expressed in both IU and the currently used units, to accustom the user to the internationally accepted new units.

17.4 The Data Sheet should make it clear that there is no fixed ratio between international standard units and the various empirical units in use at present.

18. SUPROL (SUPROFEN)

The Committee noted this paper.

19. PTMO CONFERENCE (ORAL REPORT)

Dr Mann reported on a one-day conference for PTMOs held in early May. Professor Vessey had briefed the PTMOs on his research project on myocardial

infarction in young women taking oral contraceptives. Dr Mann informed members of plans for increased use of the PTMOs for epidemiological research, for following up adverse reactions and to encourage yellow card reporting.

20. SECRETARY/MEDICAL ASSESSOR'S ORAL REPORT

None.

21. ANY OTHER BUSINESS

None.

22 DATE AND TIME OF NEXT MEETING

Thursday 26 June 1986 at 10.30 am.

GRO-C