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19/9/85.

NOT FOR PUBLICATION CSM/85/7th Meeting

COMMERCIAL IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

Minutes of the meeting held on Thursday 25 and Friday 26 July 1985, 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 A T Florence
Professor D G Grahame-Smith *
Dr J M Holt *
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

Professor D H Lawson *
Professor J O'D McGee *
Professor A E M McLean *

Dr G Jones (Medical Assessor)
Dr J Purves (Pharmaceutical Assessor)
Mr J Grimshaw (Secretary)
Mr K L Fowler (Asst Secretary)
Mr A C Cartwright *
Mr J P Digings
Dr M Duncan
Dr S Fawcett
Dr L K Fowler
Dr M Glen-Bott
Dr S Grieve
Dr A Nath
Dr J A Nicholson
Dr J M Raine *
Dr J Ritchie
Dr D I Slovick
Mr A Stewart *
Dr C Twomey *
Mr G Wade +
Dr K Winship *

* Thursday only
\+ Friday only

Also Present

Mr C Davies
Mrs M Dow *
Mr D O Hagger
Mr N Hale
Mr P C Nilsson *
Dr H Pickles
Mr C Seabrooke *

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 Elworthy, Professor Greaves, Professor Hull and Professor Vessey for both days, from Dr Castleden and Dr Ward for Thursday, and from Professor Breckenridge, Mr Darling, Professor Grahame-Smith, Dr Holt, Dr Pentecost and Dr Smith for Friday.

1.3 The Chairman welcomed Professor Lawson, who was attending on Thursday only to advise the Committee on the papers concerning efficacy requirements for products for minor conditions, and informed members that Professors McGee and McLean would be present on Thursday afternoon to give their advice on the toxicology assessment of the Somatonorm application.

1.4 The Chairman informed members that Dr Jones was acting as Medical Assessor in Dr Mann's absence, and that several members of the medical secretariat were absent owing to their attendance on a course.

1.5 The Chairman introduced and welcomed Dr Raine and Dr Slovick as new members of the Secretariat.

1.6 The Committee noted tabled paper 1, a revised agenda for the meeting.

1.7 At the start of business on Friday, the Chairman proposed that the quorum for meetings of the Committee be reduced from nine to eight and this proposal was agreed.

1.8 <u>The recent announcement by the Opren Action Group</u>

1.8.1 The Chairman made the following personal statement:

1. You will all have read recently press reports about legal actions against DHSS and the CSM on Opren. You should also have received a telephone message on Monday from the Secretariat on the subject.

2. The position is that since Opren was taken off the market a number of legal actions have been started claiming compensation for alleged damage by Opren. These actions are being coordinated by the Opren Action Committee.

3. This Committee has written to the Prime Minister making a number of allegations about the part played by the CSM and the Licensing Authority in the decisions to licence Opren and later on to revoke its licence. They also allege that there was conflict of interest on my part because some studies into Opren had been carried out in my Department.

4. The facts are that in 1978-80 staff of my Department carried out a study on gastric bleeding with Opren and flurbiprofen, financed by the Company. I gave advice on the planning of the study but was not involved in any way in the conduct of it. This role was set out on the record when the report of the study by Dr Yeung Laiwah and others, was published in 1981 in the Annals of Rheumatic Diseases. In January 1980, staff of my Department began planning a further study at the request of Eli Lilly into gastric bleeding with benoxaprofen and piroxicam. This study continued into 1982 but was never completed. I advised Dr Alan Glynne, the Company representative, that I could take no part in the Study when I became a member of the CSM and indeed I gave no advice on the study and took no part in it.

5. The Action Committee also say that I was a Member of the CSM when Opren was licensed. In fact I was not a member of the Committee when it gave its advice to licence Opren in February 1980. I was appointed to the Committee from March 1980. I was however, as Members are aware, fully involved in all the Committee's discussions leading up to the withdrawal of the product from the UK market in August 1982.

6. The complaint against me personally was of course only a small part of the accusations against the CSM and the Department which the Opren Action Committee have now put forward. These will entail considerable work for the Secretariat and the Department in replying to the plaintiff's draft statement of case. I am advised that if the case comes to court it may be one, two or three years from now before the matter is finally resolved. I will of course ensure that this Committee is kept in touch with the more significant aspects of the case.

1.8.2 Professor Grahame-Smith, on behalf of the Committee, stated that members had no doubts about the Chairman's integrity, and wanted this placed on record. Professor Weinbren said that the personal attack on the Chairman for what was a Committee responsibility was outrageous, and that the Committee would support him in any further action that may be necessary. The Chairman thanked the members for their support.

1.8.3 Mr Hale said that he was sure that members of the Secretariat would wish to be associated with the Committee's confidence in the Chairman's integrity. He informed members that the Treasury Solicitor was representing the Department and the CSM in the matter, and advised them not to comment on the case while it was sub judice. Mr Hale went on the 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 rights of members to consult their own defence society or legal advisors.

2. MINUTES OF THE MEETING HELD ON THURSDAY 27 JUNE 1985

2.1 The Committee agreed with Professor Weinbren's suggestion that item 5.3 of the Findings Section of the minutes covering the Hearing for Lodine Tablets (PL 0607/0064-66: Ayerst Laboratories) should be amended as follows:

"The Committee would be reassured on points 2 and 3 of the Section 21(1) letter provided that the indications were limited to rheumatoid arthritis. For point 1 of the Section 21(1) letter, the Committee accepted the view that the therapeutic advantage in rheumatoid arthritis outweighed the possible risk to Man. They considered that there was inadequate evidence of safety and efficacy in osteo-arthritis and other indications".

2.2 Following this amendment, the Chairman signed the minutes as a true record of the meeting.

3. MATTERS ARISING FROM THE MINUTES

3.1 Sustained Release Theophylline Preparations (and the associated applications); the Chairman informed members that it had not been possible for the July meeting of SEAR to give consideration to more detailed protocols because Professors Rowland, Elworthy and Florence had been unable to attend. The paper and applications had therefore been deferred to the September meeting.

3.2 Mr Grimshaw said that a paper discussing the policy regarding the disclosure of yellow card information, requested by the Committee, would be presented to a future meeting as the agenda was full this month.

4. CONSIDERATION OF APPLICATIONS

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

.1 Travamulsion 1% and 2%: PL 0116/0109-10: Travenol Labs.

Consideration of this application was deferred until a paper on DEHP stripping had been prepared for Committee.

4.2 Diprivan Injection: PL 0029/0190: ICI
Professor Dundee declared a specific interest and took no part in the consideration of this application.

5. WRITTEN REPRESENTATIONS

5.1 The Committee considered written representations on the following products:

5.1.1 Syrup of White Pine with Tar: PL 4776/0002: Universal Labs Ltd.

5.1.2 Human Immunoglobulin: PL 3473/0011: Scottish Health Service - Common Services Agency.

5.1.3 Chymodiactin: PL 0231/0069 and 0071: Armour Pharmaceuticals

5.1.4 Glibenclamide: PL 0058/0069-70: T Kerfoot and Co.

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 Captopril Tablets: PL 0034/0256-7: E R Squibb and Sons Ltd.

6.1.2 Fluzone: PL 0530/0127: Connaught/Harris.

6.1.3 Corvaton Tablets: PL 0086/0070: Hoechst UK Ltd.

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

7. REPORT OF THE ADVERSE REACTIONS WORKING PARTY

7.1 The Chairman, on behalf of the Committee, thanked Professor Grahame-Smith for his work as Chairman of the Working Party.

7.2 Professor Grahame-Smith presented the Report and outlined the principal recommendations. In discussion some minor changes to the Report were decided.

7.3 Subject to these amendments, the Committee agreed that the Report should be presented to Ministers.

8. EFFICACY REQUIREMENTS FOR PRODUCTS FOR MINOR CONDITIONS

8.1 The attitude of the Committee on Review of Medicines on the efficacy requirements for products for minor conditions - Paper

8.2 Review of PLRs for medicinal products for minor conditons, and the interaction with new licence applications - an overview - Paper

8.3 Cough and cold remedies - Paper

The Committee considered these three papers and noted that the application by the Licensing Authority of the policy agreed by the CRM would mean that very few products for minor conditions would be referred to them. They wanted it noted, however, that any products that were referred to them would be considered in accordance with the criteria they apply to all other products.

9. DEPO PROVERA - THE PBI REPORT

9.1 The Committee considered this paper together with a letter from Professor Elstein (tabled paper 2).

9.2 The Committee endorsed the recommendation of the SEAR Sub-Committee that the paper should be considered again when the results of the WHO report on cervical cancer among women on Depo Provera are available. In the meantime, the UK licensing position of Depo Provera should remain unchanged.

10. CARCINOGENICITY OF DIBENYLINE (PHENOXYBENZAMINE)

10.1 The Committee considered this paper. Dr Fowler informed members that the Secretariat had met the Company, as requested at the January 1985 meeting, to discuss voluntary variation of the product licence for Dibenyline Capsules (PL 0002/5009: Smith, Kline and French Labs Ltd) to restrict the indications following concern regarding the possible carcinogenic risks associated with the use of the product. A letter had been received from the company indicating that they were unwilling to do this.

10.2 The Committee endorsed the Licensing Authority's proposal that the product licence for Dibenyline Capsules be varied under Section 28 of the Medicines Act 1968 on the ground specified in Section 28(3)(g), namely that this product can no longer be regarded as one which can safely be administered for the purposes indicated in the licence, so as to restrict the indications to the treatment of hypertension due to phaeochromocytoma.

10.3 The reason for this proposal was that there is concern regarding the possible carcinogenic risks associated with the use of the product.

11. TOCAINIDE: HIGH INCIDENCE OF BLOOD DYSCRASIAS

11.1 The Committee considered this paper, and endorsed the recommendation of the SEAR Sub-Committee that the product licences for Tocainide (Tonocard Tablets and Tonocard Injection: PL 0017/016-8 and 0135: Astra Pharmaceuticals Ltd) should be revoked on grounds relating to safety because of the reported high incidence (2 per 1000) of blood dyscrasias in patients treated with the drug.

11.2 The Committee endorsed a proposal by the Licensing Authority that the product licences for the above named products be revoked under Section 28 of the Medicines Act 1968 on the grounds specified in Section 28(3)(g), namely that these products can no longer be regarded as products which can be safely administered for the purposes indicated in the licences.

11.3 The reasons for this proposal were:-

i. There is concern regarding the high incidence of blood dyscrasias reported in patients treated with Tocainide.

ii. There are no overriding clinical benefits to outweigh these risks.

11.4 The Committee considered that, in the event of revocation of the licences, the Secretariat should discuss with the Company the timing of the removal of the products from the market so that the management of patients with life-threatening arrhythmias would not be disrupted.

12. PINACIDIL (CTC 0043/0074: LEO LABORATORIES)

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

12.1 The drug was a carcinogen in the mouse, and there was no evidence to indicate that this would not imply a risk to man.

12.2 The Clinical Trial Certificate should not be renewed (renewal due in August 1985).

13. EVIDENCE OF VIRUS IN POLIO VACCINE MONKEYS (For Information Only)

The Committee noted this paper.

14. PROPOSED CALENDAR OF MEETINGS FOR 1986

The Committee noted and provisionally approved the proposed calendar.

15. SAFETY OF INTRAVENOUS IMMUNOGLOBULINS

15.1 The Committee considered this paper discussing the risk of infectivity of intravenous immunoglobulins and the reports of transmission of non A non B hepatitis by such preparations.

15.2 The Committee endorsed the recommendations of the Biologicals Sub-Committee as follows:

15.2.1 Whilst it is probably not possible to guarantee the safety of intravenous immunoglobulin preparations in respect of transmission of infection, an acceptable margin of safety is possible and will be maximised by adoption of the following procedures:

1. The use of healthy donors.

2. The testing of donor samples for evidence of infections liable to be transmitted by blood.

3. Use of the cold ethanol fractionation procedure.

4. The adoption of additional steps known to kill a variety of viruses.

5. Strict adherence to good manufacturing practice.

15.2.2 In assessing the safety of individual products the above points should be taken into account, together with the clinical evidence of safety which should include screening of recipients by means of liver function tests.

15.2.3 Tests for evidence of infection in donors are a rapidly developing field. In view of this, licensees should be asked what their plans are for screening of donors.

15.2.4 With regard to products already licensed in the UK, the Companies concerned should be asked to provide further data concerning the ability of their process to inactivate viruses, together with ongoing evidence of safety in clinical use.

16. APPEDRIN (PL 2744/0002: THOMPSON MEDICAL CO LTD) - ADVICE ON LEGAL STATUS

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

16.1 On the basis of benefit/risk considerations, Phenylpropanolamine when used as an adjunct to weight reduction and appetite control should be a Prescription-Only-Medicine.

16.2 The permanent legal status of Appedrin, which contains Phenylpropanolamine, should be POM (present legal status is P).

17. CPS AND SEAR - WORKING ARRANGEMENTS BETWEEN THEM AND WITH CSM

The Committee considered this paper and endorsed the proposed arrangements.

18. CSM UPDATES - POLICY FOR 1986

18.1 The Committee considered this paper. Dr Jones informed members of a meeting with the Editor of the BMJ, who wished to continue the CSM Update Series.

18.2 The following points were agreed:

18.2.1 The CSM Update Series should be continued in 1986.

18.2.2 An attempt should be made to produce articles that were more stimulating with more factual data.

18.2.3 The presentation of the articles in the BMJ could be improved so as not to appear promotional in design.

18.2.4 The Committee would like to see a programme for future CSM Updates at each monthly meeting.