NOT FOR PUBLICATION

COMMERCIAL IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

Minutes of the meeting held on Thursday 30 January 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 P H Elworthy
Professor A T Florence
Professor D G Grahame-Smith
Professor M W Greaves
Dr J M Holt
Professor D Hull
Dr B L Pentecost
Professor M D Rawlins
Professor M P Vessey
Dr D M B Ward
Professor H K Weinbren

Professor M J S Langman
Dr A V P Mackay
Dr G Schild

Dr A J Isaacs (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
Mr R T Clay
Miss R Coulson
Mr J Digings
Dr L K Fowler
Dr A M Glen-Bott
Dr S Grieve
Dr E R Littlewood
Dr R Mann
Dr A Nath
Dr A Nicholson
Mr M Pinel
Dr J Ritchie
Dr F Rotblat
Mr A Stewart
Dr S M Wood
Dr K Winship

Also Present

Dr G Burton
Mr R J Butcher *
Mrs M Dow
Mr D Dunleavy
Mr J Fenwick *
Mr J Griffiths
Mr D Hagger
Mr N Hale
Dr D Jeffreys
Professor Li
Mr D Lye
Mr P C Nilsson *
Dr H Pickles
Mr C Seabrooke
Mrs S Walker *

* Item 4 only

1. APOLOGIES AND ANNOUNCEMENTS

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

1.2 The Chairman informed members that Professor Langman would be attending the meeting to advise the Committee with regard to the papers on NSAIDs.

1.3 The Chairman informed members that Dr Mackay would be attending the meeting to advise the Committee with regard to the papers on Nomifensine and Mianserin.

1.4 The Chairman informed members that Mr Justin Fenwick would be attending the meeting to advise the Committee with regard to the paper on 'Discovery of Documents'.

1.5 The Chairman welcomed Dr Schild as a guest member of the Committee in place of Dr Smith.

1.6 Following the paper on 'Discovery of Documents', the Chairman introduced and welcomed Professor Li, of the Chinese Pharmacological Society, who was attending as an observer.

1.7 The Chairman congratulated Professor Jacobs, who had recently g the Watson-Smith lecture for the Royal College of Physicians.

1.8 Apologies had been received from Mr Darling (am only), Professor Jacobs and Dr Smith.

2. MINUTES OF THE MEETING HELD ON THURSDAY 19 DECEMBER 1985

2.1 Item 4.4.11 (Hearing for Actinac) was amended to read: "where were the three supportive haematologists' reports".

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

3. MATTERS ARISING FROM THE MINUTES

There were no matters arising.

4. DISCOVERY OF DOCUMENTS

4.1 The Committee considered what action should be taken in response to applications for disclosure of CSM documents made in connection with the Kinnear v Wellcome case. Professor Hull declared that he was medical adviser to one of the parties in the action, and took no part in the discussion or decision.

4.2 Mr Fenwick, Counsel for CSM, said that CSM documents had been applied for because it was felt necessary for the Court to decide what weight should be given to expert opinions, such as the Meade Panel report. The Judge would first reach a decision on the general issue of causality in relation to pertussis vaccine and brain damage, and would then go on to make a judgement in respect of Kinnear.

4.3 Mr Fenwick said that for the Court to order disclosure, the applicants had to show that the documents requested were relevant to the case and necessary for the conduct of the trial, or that they would save costs. The only basis on which disclosure could be resisted was public interest. However, even if the CSM could establish that it was against the public interest for disclosure to be ordered in such a way that the yellow card system was damaged, the Court would weigh the public interest in maintaining the yellow card system against the public interest in ensuring a fair trial. Mr Fenwick said there was a risk that the Judge would order disclosure notwithstanding the CSM's arguments against this. The Committee may, therefore, decide that it would be better to release documents voluntarily, with safeguards, rather than run the risk of an order for disclosure. Any such order would almost certainly be more comprehensive in the documents to be disclosed, and perhaps also less stringent in the safeguards on access to the data, than a voluntary agreement.

4.4 Some important safeguards might be obtained under a voluntary agreement. First, documents, and information from those documents, released in connection with the Kinnear case could only be used in that action and not in any other action. Second, an undertaking could be sought from the plaintiffs and defendants that any doctor or patient identified from released documents would not be approached. Third, released documents could be "sanitized" to remove the names, addresses, and unique identifying details of patients and doctors. Fourth, an agreement could be made that the hearing would be held in camera when details of individual cases were being discussed.

4.5 Mr Fenwick said he did not expect any disclosure arrangements made in relation to the Kinnear case to have implications for the Opren action. The cases were different in nature. The Kinnear case was essentially a test of the alleged causal connection between a medicine and damaged patients. In the Opren case the CSM was being sued on the grounds that it should not have licensed the product and did not act quickly enough to take it off the market when evidence of adverse reactions began to accumulate. There was also a practical difference between the cases in that Kinnear's legal advisers were unlikely to be representing many, if any, other claimants, whereas in the Opren case one lawyer was representing all the claimants.

4.6 Mr Fenwick asked the Committee to comment on the validity of the procedure whereby expert opinions would be tested by the Court, and for guidance on how far members wished to go in disclosing documents.

4.7 Professor Vessey said he had been a member of the Meade Panel. The Panel had put a lot of work into preparing their report and he resented that lawyers were now to re-open the data with the sole purpose of discrediting the report. He was also concerned that it would not be possible to prevent the identification of patients and doctors from released documents - no matter how carefully they were sanitized - and disclosure was, therefore, inevitably a breach of confidence.

4.8 In discussion, it was agreed that the Committee should not release unsanitized any data submitted on the understanding that it would be treated as confidential. The CSM questionnaire sent out in connection with the Meade Panel work came into this category, as did yellow cards and yellow card follow-up documents.

4.9 Concern was expressed that no matter what safeguards were applied, it might still be suggested in the media that the confidentiality of the yellow card system had been breached. It was agreed that the Committee should prepare its response to any such allegations. Drafts of a Chairman's letter and perhaps a 'Current Problems' article and a press release should be prepared.

4.10 After further discussion, the Committee agreed to the following disclosure arrangements in the Kinnear case:-

4.10.1 Single line summaries of each of the 229 cases referred to in the Meade Panel report should be released to medical and legal advisers of the plaintiffs and defendants. The summaries should not include any indication of CSM views on causality or dates of birth or any data which would enable the easy identification of the patient or doctor. The summaries based on yellow card reports would need to be re-written so that they were in the same format as the other summaries.

4.10.2 Copies of one page abstracts of specific Meade Panel cases should be released to medical and legal advisers, on request. However, details which might enable the easy identification of a case should be sanitized before issue, eg dates of birth should be removed, dates of administration and reaction should be replaced by time intervals, and the day (but not the month) of administration should be blanked out. Safeguards should be sought on the use of the abstracts and summaries.

4.10.3 If application is made for the release of the questionnaires supplied by Professor Stewart and the APVDC and they cannot be obtained from the original supplier, they should be released, with the permission of the original supplier.

4.10.4 With regard to the cases specifically requested by Dr Meade in his letter to Dr Jones (these are non-yellow card cases), the Court should be presented with the arguments against releasing the CSM questionnaire and any follow-up documents, and asked to rule on disclosure. Dr Walford's letter to doctors requesting the information should be quoted to the Court.

4.10.5 Yellow card reports and any follow-up documents, including questionnaires where they exist, should not be released. However, the Committee would release yellow card and yellow card follow-up material sanitized and transcribed to preserve anonymity, but only if the Court so ordered after hearing the arguments for and against release.

4.10.6 The Committee would not agree to providing medical advisers to the plaintiffs or defendants with access to CSM files.

4.10.7 With regard to the 42 yellow card reports, requested by Professor Stewart, a one line summary or abstract could be provided if required, subject to the conditions specified in points 4.10.1 and 4.10.2 above.

4.11 Disclosure should be subject to three safeguards:-

4.11.1 undertakings that patients or doctors identified from released documents should not be contacted;

4.11.2 documents and information from them should not be used in any other Court case;

4.11.3 the Court should be in camera when any details, enabling identification of an individual, were discussed.

4.12 Mr Fenwick said he would hold discussions with counsel for the parties in accordance with the Committee's instructions. The Committee agreed that power of decision on issues arising from the discussions should be delegated to the Chairman, and in his absence to Professor Grahame-Smith.

4.13 The Committee were advised by Mr Fenwick that it would probably be necessary for CSM affidavits to be sworn in connection with the application for disclosure. If necessary, affidavits would be sought from the Chairman, Professor Grahame-Smith, Professor Rawlins, Professor Vessey and/or Dr Ward.

5. CONSIDERATION OF APPLICATIONS

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

5.1 Sorbinil Tablets: CT 0057/0255: Pfizer Ltd.

Professor Breckenridge declared a non-specific interest.

5.2 Carbamazepine Tablets BP 200 mg: PL 0530/0149: Harris Pharmaceuticals

The Committee considered the problems of the bioavailability of Carbamazepine and asked for a position paper on the subject.

5.3 Dopamine Hydrochloride in 5% Dextrose Injection: PL 0037/0145-7: Abbott Laboratories

In connection with this application, the Committee noted tabled paper 2, a letter from the Company.

5.4 Exelderm - Sulconazole Nitrate Cream 1%: PL 0029/0185: ICI

Professor Elworthy declared a non-specific interest.

6. WRITTEN REPRESENTATIONS

6.1 The Committee considered written representations on the following products:

6.1.1 Metformin Tablets: PL 0530/0113: Harris Pharmaceuticals Ltd

6.1.2 Hismanal Suspension: PL 0232/0111: Janssen Pharmaceutical Ltd

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

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

7. THE SAFETY OF IMMUNOGLOBULIN PREPARATIONS

The Committee considered this paper, together with tabled paper 3 (report following contact with the producers of immunoglobulin preparations), and endorsed the recommendations of the Biologicals Sub-Committee as follows:

7.1 The Committee recommended, on the evidence considered, that no new licensing action to withdraw or restrict supplies should be taken in respect of intravenous or intramuscular immunoglobulin preparations.

However:

7.1.1 All immunoglobulin preparations should as soon as possible and not later than 1 July 1986 for intravenous and 31 December 1986 for intramuscular, be prepared only from donors shown to be HTLVIII antibody negative.

7.1.2 As from now, no preparations containing HTLVIII antibody in the plasma pools, bulks, or final product should be released for use.

7.1.3 Manufacturers should provide evidence of the capacity of their process to inactivate viruses by 1 July 1986 in respect of intravenous, and 31 December 1986 in respect of intramuscular immunoglobulin preparations.

7.1.4 The Committee considered that at present there was insufficient evidence to justify changing the indications for use of immunoglobulin.

7.2 The Committee recommended that close surveillance should be maintained of the development of any new virological, epidemiological or clinical data.

8. NOMIFENSINE

The Committee noted this paper, which was for information only following the decision of Hoechst (UK) Ltd to withdraw the drug from the UK market.

9. MIANSERIN

The Committee, assisted by Dr Mackay of the SEAR Sub-Committee, considered this paper and noted the recommendations of the SEAR Sub-Committee.

9.1 The Committee agreed that full blood counts should be recommended before treatment, and every four weeks for the first three months of treatment. This recommendation should appear on the data sheet.

9.1.1 In the case of agreement to voluntary amendment, the Company should be asked to send a 'Dear Doctor' letter with the amended data sheet.

9.1.2 If the Company do not agree to voluntary amendment, the Committee would advise a compulsory variation.

9.1.3 Depending on the Company's decision regarding voluntary amendment, the possibility of a 'Dear Doctor' letter from the Committee, and a 'Current Problems' article, would be considered.

9.2 The Committee asked for a position paper on the place for Mianserin in the treatment of depression, particularly whether Mianserin should be used as initial treatment for all forms of depression. It was suggested that this paper might be 'contracted out', and the Secretariat agreed to consider this.

10. NSAIDs: REPORT TO CSM ON ARGOS AD HOC MEETING (SEPTEMBER 1985)

10.1 The Chairman introduced and welcomed Professor Langman. Professor Rawlins thanked Professor Langman for attending meetings of ARGOS and for providing draft copies of his article.

10.2 The Committee considered this paper together with the following related papers:

10.2.1 'Adverse drug reactions in elderly patients (2) anti-inflammatory agents and serious gastro-intestinal reactions in the elderly' - draft paper by Dr Pickles.

10.2.2 PIROXICAM - letter from 'Public Citizen' US Health Research Group to US Department of Health.

10.2.3 PEM NEWS - summary and conclusions of a paper entitled 'A Comparative Study of Five NSAIDs'. Copies of the full paper were available for members at the meeting.

10.2.4 Draft articles for 'Current Problems' and 'CSM Update'

10.2.5 Revised draft articles for 'Current Problems' and 'CSM Update' (tabled paper 6).

10.2.6 Feldene (tabled paper 5) - letters from Pfizer to Health Ministers.

10.3 The Committee endorsed the recommendations of the SEAR Sub-Committee as follows:

10.3.1 There was an association between treatment with NSAIDs and peptic ulcer perforation and haemorrhage. The available evidence suggested that elderly patients were at a higher risk and that the risk was possibly greatest in elderly women.

10.3.2 There was concern about the suggestion that ibuprofen was safer than other NSAIDs. It was possible that if this drug was used at doses of equivalent efficacy and for the same indications as other NSAIDs, the risk of serious gastro-intestinal adverse reactions might be the same for ibuprofen as for other NSAIDs.

10.3.3 On available evidence, no individual NSAID could be regarded as either more or less toxic than any other.

10.3.4 The CSM's views on the hazards of treatment with NSAIDs should be publicised.

10.4 The Committee agreed that ARGOS should undertake a formal review of all marketed NSAIDs, and should make recommendations for any action they consider necessary, such as changes to the indications and warnings given in data sheets.

10.5 The Committee endorsed the revised draft article for 'Current Problems' (tabled paper 6) with the following amendments:

10.5.1 To be added to the first paragraph:

"Neither of these reports evaluated the effects of aspirin".

10.5.2 "NANSAIDs" to be replaced by NSAIDs".

10.6 Members agreed to consider the revised draft article for 'CSM Update' (tabled paper 6) after the meeting, and to contact the Secretary with any comments.

10.7 The Committee agreed that, if possible, the publication of the articles in 'Current Problems' and 'CSM Update' should coincide with the publication of Professor Langman's papers.

11. NSAIDs: INFORMATION REQUESTED BY CENTRAL TV (tabled paper 4)

The Committee considered this paper.

11.1 It was noted that the programme would be broadcast on March 4th.

11.2 The draft replies to Central TV's questions were discussed, and various changes were suggested. It was agreed that the Chairman should co-ordinate a redrafted version.

12. HEPATIC NECROSIS FOLLOWING MULTIPLE EXPOSURE TO HALOTHANE

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

12.1.1 The data sheet should be amended:

i. to strengthen the hepatic toxicity warnings

ii. the recommended interval between exposures should be extended to 1 year.

12.1.2 The Faculty of Anaesthetists, the Association of Anaesthetists and the Association of Dental Anaesthetists should be contacted to discuss the above recommendations, in order that their ~~medico-legal~~ implications be fully considered.

12.1.3 A 'Current Problems' article should be prepared to highlight the problems of repeated exposure to Halothane over short intervals of time.

12.2 A Licensing Authority proposal for compulsory variation of the relevant product licences was circulated as a tabled paper, and the Committee agreed to compulsory variation. Members were asked to consider the precise wording of the warning, and to contact the Secretariat with any comments.

13. ENALAPRIL

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

13.1.1 In view of the drug's capacity to cause angioneurotic oedema the drug's use should be changed from that of first line to second line therapy for all grades of hypertension.

13.1.2 The Company should be requested to inform all doctors by letter of this change in therapeutic indications.

13.1.3 A 'Current Problems' article should be prepared to discuss the problems of angioneurotic oedema associated with the drug. It should also make reference to the Company's recent letter to all doctors which gave warnings about the hypotensive and renal adverse reactions of the drug, and gave new recommendations on starting doses and initiation of treatment for congestive cardiac failure in hospital.

13.2 In the event of the Company failing to agree to voluntary variation of the relevant product licences (Innovace Tablets: PL 0025/0194-7: Merck, Sharp and Dohme), a compulsory variation would be required. A Licensing Authority proposal for compulsory variation was circulated as a tabled paper, and was endorsed by the Committee.

13.3 The Committee noted a possible association of Enalapril with blood dyscrasias, and recommended that this should be kept under review.

14. PUBLICATION ON THE POSSIBLE TERATOGENICITY OF PIPERAZINE, REFERRING TO CSM DATA

The Committee considered this paper.

14.1 The Committee agreed that the author could publish the CSM data provided that the article was accompanied by a disclaimer stating that the paper contained the views of the author alone and not the CSM.

14.2 The Committee advised that licence holders for Pripsen, Antepar, and other products containing Piperazine with similar indications and legal status, should include on the product packs a pregnancy warning compatible with that presently included in the data sheet.

14.3 The Committee noted that holders of PLRs for these products had already been notified that review will take place in 1987, and that further studies are required, including teratogenicity studies. The Committee further noted that the advice in 14.2 would not prejudice the outcome of the review.

15. INFORMATION ABOUT DRUG OVERDOSAGE

Consideration of this paper was deferred to a future meeting.

16. REFERENCE TO THE CPMP OF LICENCE APPLICATIONS FOR BIOTECHNOLOGY PRODUCTS AND "PHARMACOVIGILANCE" PROBLEMS

The Committee noted this paper, which was for information only.

17. ANY OTHER BUSINESS

17.1 National Study of Cardiovascular Deaths in Young Women (tabled paper 1)

The Committee considered this paper from Professor Vessey.

17.1.1 The Committee agreed to the reference to the CSM on notepaper for use in connection with the study.

17.1.2 It was suggested that the proposed conference for PTMOs should be widened to cover items of general interest to the CSM, and the Committee therefore agreed that the CSM should fund the conference.

17.2 Opren (tabled paper)

The Committee noted this paper, bringing members up to date on the position on the Opren litigation.

17.3 The Chairman informed members that the March 1986 meeting of CSM had been rescheduled for Wednesday 26th March (instead of Thursday 27th March).

18. SECRETARY/MEDICAL ASSESSOR'S ORAL REPORT

None.

19. DATE AND TIME OF NEXT MEETING

Thursday 27th February 1986, at 10.30 am.