NOT FOR PUBLICATION

COMMERCIAL IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

Minutes of the meeting held on the afternoon of Wednesday 27 May and on Thursday 28 May 1987, in the 19th Floor Conference Suite, Market Towers.

Present

Professor A W Asscher (Chairman)*
Professor M D Rawlins ++
Professor A M Breckenridge
Dr T G Booth +
Professor J G Collee
Professor P H Elworthy
Professor A T Florence
Professor M W Greaves
Dr W A Jerrett
Professor M J S Langman *
Professor D H Lawson *
Mr F E Loeffler
Professor J O'D McGee
Professor A E M McLean *
Dr Elizabeth Mayne
Professor S R Meadow
Dr S A Montgomery
Professor G Nuki
Dr B L Pentecost
Professor M P Vessey

~~Guest~~ Members for the Day
Professor A M Geddes +
Professor J M Newton +
Dr G Schild *

Dr D Jefferys (Medical Assessor)
Dr R D Mann (Medical Assessor, Adverse Reactions)
Dr J Purves (Pharmaceutical Assessor)
Miss A Simkins (Secretary)
Mr K L Fowler (Assistant Secretary)
Mr A Akin-yele
Dr G Burton
Dr T Corn
Miss R Coulson
Dr D Looi
Dr L K Fowler
Dr A Glen-Bott
Dr S Grieve
Mr J Grimshaw
Miss S Harris
Miss D Hepburn
Dr J Hilton
Mr J McCracken
Dr J A Nicholson
Mrs M Noble
Dr J Raine
Dr J Ritchie
Dr F Rotblat
Dr D Slovick
Dr K Winship
Dr S Wood

Also Present
Mr D Dunleavy
Mr D Hagger
Dr J Yeo
Ms J Mayhew
Dr A Watt
Mr C Wilson

++ Chairman on Wednesday
+ Wednesay only
* Thursday only

1. APOLOGIES AND ANNOUNCEMENTS

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

1.2. Apologies for absence had been received from Professor Jacobs, Professor MacLean, Professor Langman and Professor Nuki for the Wednesday afternoon session, and from Professor Jacobs for Thursday.

1.3. Professor Rawlins (Chairman on Wednesday) welcomed Professor Geddes as and Professor Newton to the Wednesday session, which they were attending ~~to advise the Committee on~~ the Zinnat Hearing.
members for the day for

1.4. Professor Asscher welcomed Dr Schild to the Thursday meeting which he was attending to introduce the findings and recommendations of the Biologicals Sub-Committee.

1.5. The Chairman welcomed back to the Medical Secretariat Dr June Raine, after the birth of her ~~son~~ daughter.

1.6. The Chairman congratulated Professor Rawlins on his recent election to the Fellowship of the Royal College of Physicians of Edinburgh.

2. MINUTES OF THE LAST MEETING

2.1. The following amendments were made to the minutes.

- Item 1.9, third line should read: Chairman of the DHSS Advisory Committee on Breast Screening

- Hearing - Normax, PL 0038/0092, Bencard, Pg 53 Line 5: insert 'no' between 'that' and 'no-effect'.

- Hearing Normax, Pg 55, No 5 Findings lines 2 and 3 of point 1 should read: 'Constipation in geriatric practice and in analgesic induced constipation in the terminally ill for all age groups.'

2.2. Following these amendments the minutes were agreed and signed by the Chairman as a true record of the meeting.

3. MATTERS ARISING FROM THE MINUTES

3.1. The Chairman raised the issue of naming individual members in the minuted reports of hearing procedures. Members expressed the opinion that contributions from individual committee members should not in future be identified since the decisions were those of the Committee as a whole.

3.2. Halothane: The Chairman informed members that Professor Rosen had now written to the BMJ admitting that he was in error.

3.3. Felbinac Gel; Professor McLean was concerned that the preclinical toxicological expert report was misleading with regard to mutagenicity data. He noted that there had been a similar concern over the mutagenicity data for Ceretec. Dr Jefferys said that the Licensing Authority was investigating the issue raised in the Felbinac pre-clinical expert report and would take appropriate action. The Committee would be given a full paper on Ceretec mutagenicity at the June meeting.

4. APPLICATIONS

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

4.2. Rocephin Vials 250, 500 mg: PL 00331/0169-72: Roche Products Ltd
Professor McGee declared a direct non-specific interest and did not speak.

4.3. Engerix B Vaccine: Pl 0002/0160: Smith, Kline & French

4.3.1. Professor Langman and Professor Nuki declared direct non-specific interests and did not speak. Professor Vessey and Professor McGee declared indirect non-specific interests which did not debar them from speaking.

4.3.2. The Committee commended the quality of the report and work on the chemistry and pharmacy aspects of this application, and asked the Chairman to communicate this to the Company.

4.4. Aarane: PL 0113/0111: Fisons plc

Professor Rawlins declared a direct non-specific interest and did not take part in the discussion. Professor Breckenridge therefore presented the recommendations of the SEAR Sub-Committee. Professor Langman declared an indirect non-specific interest which did not debar him from speaking.

4.5. Felodipine Tablets 5, 10 mg: PL 0017/0235-6: Astra Pharmaceuticals

Professor Langman and Dr Jerrett both declared indirect non-specific interests which did not debar them from speaking.

4.6. Kliogest: PL 4668/0013: Novo Industries Ltd

Dr Montgomery declared an indirect non-specific interest which did not debar him from speaking.

4.7. Pregnavite Forte F: PL 0038/0339: Beechams Pharmaceuticals

4.7.1. Professor Breckenridge declared a direct non-specific interest but spoke with the Chairman's permission. Professor Collee declared an indirect non-specific interest which did not debar him from speaking.

4.7.2. Members agreed that the Chairman should communicate the Committee's decision to the MRC (because of their on-going trial) at an appropriate time, when the licensing procedure had been completed.

WRITTEN REPRESENTATION

5.1. The Committee considered a written representation on the following product:- Lupron Injection: PL 0037/0184: Abbott Laboratories Ltd

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

6. HEARING

6.1. The Committee held a hearing on the following product:

Zinnat Tablets: PL 004/0317-8: Glaxo Laboratories

6.1.1. The Committee proceedings for this hearing were chaired by Professor Rawlins as Professor Asscher had declared an indirect, specific interest and was not present for the hearing.

6.1.2. Professor Nuki and Dr Montgomery both declared direct non-specific interests and did not speak. Dr Booth and Professor Florence both declared indirect non-specific interests which did not debar them from speaking.

6.2. The Committe also considered additional data on the following product, the Companies having withdrawn from the scheduled hearing at the last moment.

Desensitising Allergens: PL 0055/5001, 0051, 0053, 0055-6: Miles etc

6.2.1. Professor Collee declared an indirect non-specific interest which did not debar him from speaking. Professor Langman declared a direct specific interest and did not take part in the discussion.

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

7. DESENSITISING VACCINES (PAPER)

The Committee noted this paper and determined that their advice to the Licensing Authority for all other extant product licences for desensitising vaccines should be the same as that for Miles (see Annex C).

8. DRAFT CPMP EFFICACY GUIDELINES ON CLINICAL TRIALS IN CHILDREN, CLINICAL TRIALS IN THE ELDERLY AND ON THE CLINICAL INVESTIGATION OF ANTIDEPRESSANT DRUGS

The Committee noted the paper and tabled paper 2 containing letters from Dr MacKay and Professor Meadow. Dr Montgomery had also written to Dr Jefferys. Members were invited to send comments to Dr Jefferys who would transmit them to the CPMP.

9. DRAFT CPMP SAFETY GUIDELINES ON THE REQUIREMENTS FOR THE PRE-CLINICAL BIOLOGICAL TESTING OF MEDICINAL PRODUCTS DERIVED FROM BIOTECHNOLOGY

The Committee considered this paper. Any comments from members were to be sent urgently in writing to Dr Wood.

10. DRAFT CPMP GUIDELINES FOR RECOMBINANT DNA PRODUCTS AND FOR MONOCLONAL ANTIBODIES

The Committee noted this paper.

11. LORAZEPAM AND WITHDRAWAL PHENOMENA

The Committee considered this paper and agreed that there was a problem regarding the safe and effective use of benzodiazepines. The Committee authorised the secretariat to obtain voluntary agreement on the revision of the lorazepam data sheets in line with the recommendations of the SEAR Sub-Committee. A proposal from the Licensing Authority on the compulsory variation of the Lorazepam licences was tabled, but the Committee agreed that action on compulsory variation should not be taken at this stage, pending a wider review.

Members were informed that a conference organised by Dr Montgomery under the auspices of the Royal College of Psychiatrists would take place on June 10; CSM would be informed of the decisions of that conference at the June meeting and would consider further action on benzodiazepines.

12. NSAID-INDUCED ASTHMA: RELEVANCE TO LABEL WARNINGS ON OTC PACKS OF IBUPROFEN

The Committee agreed that there should be a warning to asthmatics on the patient information leaflets and labels of over the counter ibuprofen products. The Committee noted that there were already 10 label warnings on the ibuprofen packs. They therefore felt that it would be appropriate to ask the Secretariat to discuss a suitable warning with PAGB. The Committee recognised that they might need to readdress this issue in the light of the discussions with PAGB.

The Committee also endorsed the recommendations of the SEAR Sub-Committee that the cooperation of the PSGB should be sought in informing the pharmaceutical profession, and that a Current Problems article should be written to inform the medical and pharmaceutical professions of the potential dangers associated with the use of NSAIDS by asthmatics.

13. GUIDELINES FOR COMPANY SPONSORED POST-MARKETING SURVEILLANCE

Paragraph 1 of the guidelines was amended to read as follows:-

> These guidelines are intended for Post-Marketing Surveillance (PMS) observational cohort studies sponsored by pharmaceutical companies.

Following this amendment the Committee considered the paper, endorsed the recommendations of the SEAR Sub-Committee and asked that the guidelines be reviewed after 18 months operation.

14. POST-MARKETING SURVEILLANCE - A REVIEW

Members discussed the paper which had been prepared by Professors Rawlins and Breckenridge. A note of the discussion is at Annex D.

It was decided to set up a working group to consider the role of CSM and other bodies in post-marketing surveillance, including an assessment of current and developing initiatives and methodologies, and to make recommendations to the Committee.

Professors Asscher, Breckenridge, Florence, Langman, Lawson, Rawlins and Vessey agreed to take part. Dr Mann would convene a meeting as soon as possible.

15. RED ALERT SCHEME

The Committee endorsed the concerns expressed in the recommendations of the SEAR Sub-Committee and authorised the Chairman to open informal discussions with Professor Inman, using the good offices of Sir Douglas Black, in order to discourage Professor Inman from continuing with his Red Alert proposals. Professor Asscher would report his discussions to the next CSM meeting.

16. ABPI TRIPLICATE YELLOW CARD PROPOSALS

The Committee noted this paper.

17. THE NEED FOR VALIDATION OF IN VITRO SCREENING TESTS FOR VIRAL CONTAMINATION OF BLOOD DONATIONS USED IN THE MANUFACTURE OF BLOOD PRODUCTS

The Commitee considered this paper and endorsed the recommendations of the Biologicals Sub-Committee.

18. CSM ON VIDEO

The Committee discussed ideas for making one or more videos to promote the work of the CSM and the Licensing Authority. A video team was present to film the Committee at work for inclusion in the ABPI's video 'An Acceptable Risk' after appropriate steps had been taken to ensure confidentiality of commercially sensitive data.

19. SECRETARY'S PROGRESS REPORT

19.1. The Committee noted the Secretary's Report. Professor Breckenridge drew members' attention to the information about additions to the ADR register which ARGOS had asked Miss Simkins to present to CSM every month.

19.2. Miss Simkins referred to a court hearing concerning the apportionment of costs in the Opren action. The plaintiffs' appeal against the decision would be heard on 2 June; the outcome would be reported to the next meeting.

20. ANY OTHER BUSINESS

None

21. DATE AND TIME OF NEXT MEETING

Thursday 25 June 1987 at 10.30 am.

GRO-C

Number

PL 0031/0169-72

Company

Roche Products Ltd

Product

Rocephin Vials
250, 500 mg
1 and 2 g

Therapeutic

Antibiotic

Active Constituent

Ceftriaxone,
disodium
3.5 hydrate

MAIN COMMITTEE 28 May 1987

ADVICE

On the evidence before them the Committee advised the grant of Product Licences for this preparation on condition that:

1. The data sheet is amended to mention prolonged prothrombin time as a side effect and to reflect the occurrence of pseudomembranous colitis after single dose administration.

Active Constituent

2. The active constituent specification is revised in the following aspects;

   2.1. limits for specific rotation are tightened,

   2.2 limits for total and all named impurities are revised in the light of recent batch analyses,

   2.3 the limit for residual solvent is reduced or justified.

3. Satisfactory details of reaction conditions and yield for the final synthetic step are provided.

Dosage Form

4. The finished product specification is revised in the following aspects;

   4.1 the proposed check assay limit is raised or justified,

   4.2 assurance is provided that the product will meet the requirements of Ph Eur pyrogen test, when tested,

   4.3 a suitable related substance test with satisfactory limits is included.

5. The proposed overage in the finished product is reduced or justified.

6. Validation data in relation to the filling of vials are provided.

Remark to the Company

The concentration of solutions used to test pH should be clarified.

Remark to Licensing Authority.
Any abridged application or variation to extend the use of the product beyond single dose should be

Number

PL 0002/0160

Company

Smith, Kline & French

Product

Engerix B Vaccine

Therapeutic

Vaccine

Active Constituent

Hepatitis B Surface Antigen

MAIN COMMITTEE 28 May 1987

ADVICE

On the evidence before them the Committee advised the grant of a Product Licence for this preparation on condition that:

1. The data sheet is amended to the satisfaction of the Secretariat.

2. An assurance is provided that information on the stability of the cell banks will be provided as it becomes available.

3. A specification for antigen protein ratio is included in the specification for the non-adsorbed bulk.

4. Full specifications for substances used in the fermentation are supplied.

5. The product licence is subject to the control of a Full Stop Order (Type A).

6. Satisfactory preservative efficacy data are provided.

7. The product labels and literature state 'protect from light'.

Remarks to the Company

1. The proposed fermentation scale-up to 1600 litres will require a variation to the Product Licence. Full supporting data to validate this change will need to be provided.

2. The expert report on the preclinical studies should discuss the scientific reasons for not undertaking toxicology studies. The explanation that studies were not done because of the results of discussions with the Secretariat is not acceptable.

3. The company should contact the BP Secretariat concerning the need for an approved name.

X1061.3

Number

PL 0086/0123

Company

Hoechst UK

Product

Rabipur

Therapeutic

Rabies Vaccine

Active Constituent

MAIN COMMITTEE 28 May 1987

ADVICE

On the evidence before them the Committee advised the grant of a Product Licence for this preparation on condition that:

1. Further adequate information on the method of manufacture and in process controls and tests, with appropriate validation are given. Where necessary appropriate limits should be applied to in process controls and tests.

2. Legible stability data are provided which should be more detailed and include information on antigen content. The shelf life after reconstitution should be indicated. The effect of light should be discussed.

3. Adequate information on the diluent is provided.

4. Sample labels which conform with the labelling regulations are provided.

5. The data sheet is amended to the satisfaction of the Secretariat with particular regard to:

   5.1 The pregnancy warning for prophylactic and post exposure vaccination.

   5.2 The route of administration of concomitant immunoglobulin.

   5.3 The egg allergy warning for post exposure vaccination.

6. The batch release procedure will apply and, where appropriate, samples of reference standards will be supplied to NIBSC.

X1061.13

Number

PL 0095/0118

Company

Cyanamid

Product

Prostap 1 mg/ 0.2 ml Pre-filled Syringe

Therapeutic

Treatment of Prostatic Cancer

Active Constituent

Leuprorelin Acetate

MAIN COMMITTEE 28 May 1987

ADVICE

On the evidence before them the Committee had reason to think that on grounds relating to safety, quality in relation to safety and quality in relation to efficacy 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 data sheet should be amended as follows:

   1.1 Uses - treatment should be restricted to patients with advanced prostatic cancer.

   1.2 Warnings - these should be amended to the satisfaction of the Secretariat: the risk of 'disease flare' during the first two weeks of treatment should be emphasised; recommendations as to how this risk could be minimised should be included.

Drug Substance

2. The formation of potential impurities, including truncated and modified peptides, at each stage of synthesis should be discussed and evidence presented that the analytical procedures employed will detect them.

3. Information should be given on any differences in the impurity profile in leuprorelin acetate synthesised using purchased intermediates or by using different purification methods. The name and address of the Takeda subsidiary supplying the purchased intermediates should be given.

4. Specifications for Key intermediates should be tightened or justified.

5. Information should be provided on palladium levels at the end of synthetic step 10 and in leuprorelin acetate and unless otherwise justified a limit for palladium applied to the specifications.

6. Further evidence of structure should be provided.

7. Adequate characterization of the reference standard for leuprorelin acetate should be provided. Which reference standard is used should be indicated.

Number

PL 0095/0118

Company

Cyanamid

Product

Prostap 1 mg/ 0.2 ml Pre-filled Syringe

Therapeutic

Treatment of Prostatic Cancer

Active Constituent

Leuprorelin Acetate

8. Batch analyses should be provided for material used for toxicological and clinical studies and for recent production batches. The results should include levels of individual impurities.

9. The specification for the drug substance should be reviewed in the light of recent production batch analyses and should include:

   9.1 A specific assay with suitable limits.

   9.2 Appropriate limits for specified impurities.

   9.3 A tighter limit for amino acid analysis.

   9.4 A tighter limit for moisture.

   9.5 Optical rotation measured on the anhydrous material.

   9.6 A tighter limit for residue on ignition.

   9.7 An acetic acid determination with suitable limits.

   9.8 The content of the active constituent should be expressed in terms of the anhydrous acetic acid free basis.

10. Limits for residual reagents and solvents should be included in the specification or their absence justified.

Dosage Form

11. Specifications for the final container should be given.

12. Methods of sterilization of the final container should be given with appropriate validation.

13. Information should be provided on the specificity of the HPLC assay for leuprorelin acetate.

14. Batch analyses for recent production batches should be provided.

15. The finished product specifications for the pre-filled syringe should be reviewed in the light of recent production batch analyses and should include

   15.1 A tighter specification for the content of leuprorelin acetate.

Number

PL 0095/0118

Company

Cyanamid

Product

Prostap 1 mg/ 0.2 ml Pre-filled Syringe

Therapeutic

Treatment of Prostatic Cancer

Active Constituent

Leuprorelin Acetate

15.2 Appropriate limits for specified impurities.

15.3 A test for abnormal toxicity.

15.4 The content of the active constituent should be expressed in terms of leuprorelin mono-acetate and in the equivalent amount of peptide base.

16. The batch release procedure should apply and in addition samples of the reference standard should be supplied to NIBSC.

17. Sample labels for the container and outer package should be provided and package inserts should also be provided. Adequate storage instructions should be given and the content of the active constituent should be expressed in terms leuprorelin mono-acetate and in the equivalent amount of peptide base.

18. Stability.

18.1 Stability data using leuprorelin acetate from both purification methods should be provided.

18.2 Levels of impurities and degradation products should be provided.

18.3 Information on the effect of light should be provided.

18.4 Further data on the pre-filled syringe should be provided to justify the proposed shelf life.

18.5 Details of storage conditions used in stability studies should be provided.

18.6 Information on any change in the syringe volume on storage should be provided. The significance of any change should be discussed.

19. Details of the methods of sterilization of equipment used in manufacture should be provided.

20. It should be confirmed that the Bio-sil ODS 5S column is used for the HPLC assay for leuprorelin acetate.

Remark

Concerning the risk of "disease flare": any recommendations as to how this risk could be minimised should be supported by evidence as to the efficacy of the recommended regimen.

Number

PL 0113/0111

Company

Fisons plc

Product

Aarane

Therapeutic

Bronchodilator

Active Constituent

Reproterol hydrochloride
Sodium cromoglycate

MAIN COMMITTEE 28 May 1987

ADVICE

On the evidence before them the Committee had reason to think that on grounds relating to safety and efficacy 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. There was inadequate evidence that both ingredients together were more effective than each ingredient on its own.

2. The data sheet should be modified to include an adequate pregnancy warning.

3. A new name should be agreed with the Secretariat which would not be easily confused with 'Aerrane' (isoflurane anaesthetic).

X1061.5

Number

PL 0017/0235-6

Company

Astra
Pharmaceuticals

Product

Felodipine Tablets
5 and 10 mg

Therapeutic

Vasodilator
Calcium antagonist

Active Constituent

Felodipine

MAIN COMMITTEE

28 May 1987

ADVICE

On the evidence before them the Committee had reason to think that on grounds relating to safety, quality and efficacy they would be unable to advise the grant of Product Licences 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. There was concern regarding the colonic hyperplasia seen in animals.

2. Reassurance was required about the lack of mutagenic potential of felodipine. There was concern over the interpretation of the tests undertaken. A test for chromosomal aberrations in mammalian cells in vitro should be performed to complete the package recommended in the guidelines.

3. There was concern over the poor survival in the mouse carcinogenicity study. The cause of this was uncertain. There was concern about the increased incidence of liver tumours.

4. There was concern over the hyperplasia of the oesophageal groove seen in the rat carcinogenicity study.

5. There was concern about the breast hyperplasia seen in the mothers in the reproductive studies.

6. There was concern about the bile duct hyperplasia in the rat.

7. There is insufficient evidence of efficacy for felodipine as a single agent at doses with a favourable adverse reaction profile.

8. There was concern that the degree of selectivity claimed would not occur at therapeutic doses.

9. The lack of effect on myocardial contractility referred to in the data sheet should be substantiated.

10. There was concern regarding the potential for drug interactions.

11. An overall analysis of adverse reactions to Felodipine should be provided.

Number

PL 0017/0235-6

Company

Astra
Pharmaceuticals

Product

Felodipine Tablets
5 and 10 mg

Therapeutic

Vasodilator
Calcium antagonist

Active Constituent

Felodipine

12. If Felodipine were to be used as monotherapy for angina the Committee would wish to be reassured about the lack of exacerbation of existing angina.

13. The data sheet should be amended to the satisfaction of the Secretariat.

14. The limits for impurities in the active constituent specification should be tightened or justified.

15. The limits in the finished product specification for the degradation product (H152/37) and the check assay should be tightened or justified.

Remark to Company

The chemical name should include a satisfactory indication of the racemic nature of the active constituent.

Number

PL 0039/0222-4

Company

Evans Medical Ltd

Product

Prazosin Hydrochloride Tablets 0.5, 1 & 2 mg

Therapeutic

Antihypertensive

Active Constituent

Prazosin Hydrochloride

MAIN COMMITTEE 28 May 1987

ADVICE

On the evidence before them the Committee had reason to think that on grounds relating to safety, quality and efficacy they would be unable to advise the grant of Product Licences 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. In vivo bioavailability studies of sufficient power were required to compare all tablet strengths to the UK market leader.

Drug Substance - To be addressed to Fermion

2. A full specification for 3,4-dimethoxy-6-isothiocyanato benzonitrile should be provided including control of potential isomeric impurities.

3. The drying conditions used in the final purification stage should be specified and evidence provided that these conditions ensure the removal of residual solvent.

4. Drug Substance specification

4.1 A more stringent control on the appearance of the substance should be included.

4.2 An appropriate related substances test with limits for potential impurities should be included.

The method should be shown to separate potential impurities from the synthetic route and from degradation. The sensitivity of the method should be stated. The limits set should be supported by batch analytical results.

4.3 Clarification should be provided of the tests routinely carried out on the drug substance.

4.4 Limits for the assay, sulphated ash and nickel should be tightened or justified.

4.5 References to the USP should be updated to the current edition, where relevant.

Number

PL 0039/0222-4

Company

Evans Medical Ltd

Product

Prazosin Hydrochloride Tablets 0.5, 1 & 2 mg

Therapeutic

Antihypertensive

Active Constituent

Prazosin Hydrochloride

5. Satisfactory information should be provided on the level at which other polymorphs can be detected by the methods described in the specification for prazosin hydrochloride.

6. Characterization of the reference standard should be provided.

7. Stability data on the drug substance should be provided including the level of related substances and confirmation of polymorphic form.

Dosage Form - To be addressed to Evans

8. Dissolution profiles of the batches used in the bioavailability studies should be provided and data should cover a 45 minute period. Information on the reproducibility of all reported dissolution profiles should be provided.

9. A test for related substances should be included in the finished product specification.

Remarks to Company (Evans)

1. If bioequivalence is not demonstrated, pharmacodynamic studies in hypertensive patients may be used to demonstrate safety.

2. Further differentiation of the tablet strengths should be considered.

Number

PL 0530/0224-7

Company

Harris Pharmaceuticals Ltd

Product

Prazosin Hydrochloride 0.5, 1, 2 & 5 mg

Therapeutic

Antihypertensive

Active Constituent

Prazosin Hydrochloride

MAIN COMMITTEE 28 May 1987

ADVICE

On the evidence before them the Committee had reason to think that on grounds relating to safety, quality and efficacy they would be unable to advise the grant of Product Licences 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. In vivo bioavailability studies of sufficient power were required for all tablet strengths against the UK market leader.

Drug Substance

2. Controls should be introduced on potential isomeric impurities of the starting material 3,4-dimethoxybenzonitrile.

3. Confirmation should be given of the method used routinely for testing for related substances. The method should be appropriate for the route of synthesis used.

4. Satisfactory information should be provided on the level at which other polymorphs can be detected by the methods described in the specification for prazosin hydrochloride.

5. In stability studies, the level of related substances found should be quantified, and the polymorphic form confirmed after storage.

6. Batch analyses of recent batches should be provided to demonstrate acceptably low levels of residual solvents when determined using specific methods.

7. The specification for prazosin hydrochloride should include a limit on heavy metals.

8. The assay limit for prazosin hydrochloride and the limit on individual related substances should be tightened or justified.

Dosage Form

9. Satisfactory dissolution data should be provided for aged product when tested using the current dissolution methodology.

Number

PL 0530/0224-7

Company

Harris Pharmaceuticals Ltd

Product

Prazosin Hydrochloride 0.5, 1, 2 & 5 mg

Therapeutic

Antihypertensive

Active Constituent

Prazosin Hydrochloride

10. Quantitative solubility data should be presented for prazosin hydrochloride (β form).

Remarks

1. If bioequivalence is not demonstrated, pharmacodynamic studies in hypertensive patients may be used to demonstrate safety.

2. The specification and test methods for the active constituent and the finished product, should not refer to BP Methods which are specific to a monograph until that monograph has been published.

3. Attention should be paid to the clarity and quality of the presentation of data as graphs and tables.

Number

PL 0549/0054-5

Company

Regent Laboratories Ltd

Product

Tamoxifen Citrate Tablets BP 10 and 20 mg

Therapeutic

Antioestrogen

Active Constituent

Tamoxifen Citrate BP 10 and 20 mg

MAIN COMMITTEE 28 May 1987

ADVICE

On the evidence before them the Committee had reason to think that on grounds relating to safety, quality and efficacy they would be unable to advise the grant of Product Licences 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. There was a need for in vivo bioequivalence data from a properly controlled comparison with the market leader in humans.

Drug Substance

2. The polymorphic form used should be specified and routinely controlled by a suitable technique.

Dosage Form

3. Additional stability data should be provided for future batches on an on-going basis, showing

   3.1 the content of Tamoxifen by a suitable stability-indicating technique

   3.2 quantitative levels of the E-isomer and related substances.

Number

PL 4668/0013

Company

Novo Industries Ltd

Product

Kliogest

Therapeutic

Hormone Replacement Therapy

Active Constituent

Oestradiol
Oestriol
Norethisterone Acetate

MAIN COMMITTEE 28 May 1987

ADVICE

On the evidence before them the Committee had reason to think that on grounds relating to safety and efficacy 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 rationale for the combination had not been justified.

2. There was inadequate evidence of efficacy in the proposed indication.

3. The high frequency of breakthrough bleeding in post-menopausal women after the first few months of treatment was unacceptable.

4. The frequency of mastalgia appeared unacceptably high.

5. The clinical consequences of continuous progestogen therapy in this group of patients had not been established.

X1061.10

Number

PL 0038/0339

Company

Beecham Pharmaceuticals

Product

Pregnavite Forte F

Therapeutic

Vitamin & Mineral Supplement

Active Constituent

MAIN COMMITTEE 28 May 1987

ADVICE

On the evidence before them the Committee advised the grant of a Product Licence for this preparation.

Number

PL 0607/0076-7

Company

Ayerst Laboratories Ltd

Product

HRF Ayerst 100 and 500 mcg

Therapeutic

Hormone for treatment of infertility

Active Constituent

Gonadorelin Hydrochloride (Hypothalamic Releasing Factor)

MAIN COMMITTEE 28 May 1987

ADVICE

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

Drug Substance:

1. Satisfactory specifications should be supplied for all starting materials reagents and solvents used in the synthesis of gonadorelin.

2. The formation of potential impurities, including truncated and modified peptides at each stage of the synthesis should be discussed and evidence provided that the analytical procedures employed will detect them.

3. The specifications of the key intermediates at Stages XXV and XX should include

   3.1 tighter limits for the purity of the intermediates,

   3.2 tests and limits for the content of specified impurities including reagents, solvents, synthetic precursors, catalysts and related impurities, or their absence justified, and

   3.3 tests and limits for the specific optical rotation of each of these intermediates or their absence justified.

4. The reference standards used should be suitably characterized.

5. The routine use of HPLC analysis of peptide content in place of biological assay of the potency of gonadorelin should be experimentally justified by comparison with the BP biological assay for gonadorelin.

6. Certificates of analyses should be provided for three representative batches of the drug substance purified by each of the stated methods.

Number

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Therapeutic

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Active Constituent

Gonadorelin Hydrochloride (Hypothalamic Releasing Factor)

7. An assurance should be given that, when tested, the drug substance will comply with the current BP monograph for Gonadorelin.

8. Satisfactory evidence of the identity of the drug substance and content of named impurities should be provided.

9. Satisfactory evidence of the stability of the drug substance should be provided.

Dosage Form:

10. Complete details of the method of sterilization of equipment, vials and caps should be provided.

11. An assurance should be given that the porosity of the sterilizing filter is not greater than 0.2 microns and that these filters are tested for integrity before and after use.

12. An assurance should be given that the reconstituted product will, when tested, comply with the BP monograph for Gonadorelin Injection.

13. Satisfactory evidence should be provided on the efficacy of the chosen preservative system over the period of therapeutic use for fresh and aged samples of the reconstituted product tested in accordance with BP guidelines. The results of preservative assays should also be reported.

14. Product literature:

    14.1 Copies of the proposed label, carton, package insert and a complete data sheet should be provided and found to be satisfactory.

    14.2 The label and product literature should state clearly the period after which the reconstituted product should be discarded. This time period should be justified.

    14.3 The product literature should specify suitable administration equipment of proven compatibility with the product.

15. Active substance vial:

    15.1 The manufacturing overage of 5% should be justified.

    15.2 Confirmation should be given that the vials would comply with BP requirements for uniformity of weight, if tested.

Number

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15.3 The wide pH limits in the product specification should be narrowed or justified.

15.4 The limits in the specification for content of gonadorelin should be tightened at release.

15.5 A test and limits for impurities and degradation products of gonadorelin should be included in the product specification.

15.6 Evidence should be provided to demonstrate that the HPLC assay of gonadorelin used during stability studies is suitably stability-indicating.

15.7 A specification should be provided for the butyl rubber of the vial stopper.

15.8 An assurance should be given that, when tested, Lactose will comply with the BP monograph.

16. Diluent ampoule:

16.1 The manufacturing formula for batches of the benzyl alcohol diluent should be supplied.

16.2 An assurance should be given that diluent ampoules are checked for particulate contamination and uniformity of content according to the BP methods.

16.3 The wide pH limits in the specification for the diluent should be narrowed or justified.

16.4 The limits for the release assay of benzyl alcohol content should be narrowed or justified.

17. On importation to the UK the product and diluent should be tested to the full finished product specifications.

18. The routine use of HPLC analysis of peptide content in place of biological assay of the potency of gonadorelin should be experimentally justified by comparison with the BP biological assay for gonadorelin.

19. The data sheet should be amended to the satisfaction of the secretariat.

20. The product licence should be subject to the control of batch release procedures with stop on sale (Stop Order, Type A).

COMMERCIAL IN CONFIDENCE

NOT FOR PUBLICATION

CSM/87/5th Meeting
CSM/SEAR/87/5th Meeting
CSM/BIOLS/87/5th Meeting

COMMITTEE ON SAFETY OF MEDICINES
SUB-COMMITTEE ON SAFETY, EFFICACY AND ADVERSE REACTIONS
SUB-COMMITTEE ON BIOLOGICAL PRODUCTS

WRITTEN REPRESENTATION 1

PL 0037/0184

LUPRON Injection 5 mg/ml

Abbott Laboratories Ltd

Active Constituent: Leuprorelin Acetate.

Therapeutic Class: Nonapeptide for the treatment of advanced prostatic cancer.

Medical Assessor: J Nicholson

Pharmaceutical Assessor: B Woollett

1. BACKGROUND

1.1. An application for a product licence for this product was received on 28th October 1985.

1.2. The application was considered by the Committee at their meeting in March 1986. The Committee 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. (This application was considered by the sub-committee on biological materials in March 1986).

1.3. The Committee provisionally concluded that:

1. The practice of filling recovered solution should be stopped or justified.

2. A non-specific toxicity test should be included in the Finished Product Specification.

3. The data sheet should be amended to the satisfaction of the secretariat. The 'Warnings' section should emphasise the risk of disease flare in the first two weeks of Lupron therapy.

4. Evidence should be provided to show how the risk of disease flare in the first two weeks of Lupron therapy could be minimised.

5. The batch release procedure should apply and in addition samples of reference standard should be supplied to NIBSC.

Drug Substance

6. The formation of potential impurities, including truncated and modifipeptides, at each stage of synthesis should be discussed and evidence that the analytical procedures employed will detect them.

7. A test for palladium content should be included in the specification for pGly-His-Trp-Ser-Tyr-D-Leu-Leu-Arg (MBS)-ProNHEt, produced by step 10.

8. Satisfactory specifications should be provided for all solvents and reagents used in the synthesis of the drug substance.

9. The specification for key intermediates, from steps 3, 9 and 10 should be tightened.

10. The limits for the specification for the amino acid analysis, and for the assay of the drug substance should be tightened of justified.

11. Confirmatory tests for impurities in addition to HPLC and TLC should be included in the drug substance specification.

12. The drug substance specification limits for individual impurities should be justified by the provision of results of consecutive batch analysis and tightened if necessary.

13. Satisfactory explanation should be provided for the lack of correlation between results on impurity levels from HPLC and TLC.

14. The wide moisture limits in the raw material specification should be tightened or justified.

15. The optical rotation measurements should be carried out on anhydrous material.

16. The limit for residue on ignition should be reduced or justified.

17. Legible photocopies of TLC plates and table III referred to on page 49 should be provided.

Dosage Form

18. The choice of a multiple dose vial presentation should be justified.

19. Tests for abnormal toxicity and for pyrogens shuld be included in the finished product specification.

20. Information should be provided on the absorption of leuprolide onto plastic syringes.

21. The draft label should be amended to include the warnings store in a refrigerator (2-8°), protect from light, and discard 14 days after first use.

22. Definitive information is required on which is the current reference standard material, and details of its impurity profile and assay results should be provided.

23. The data from USP prservative efficacy test should be provided and should be found to be satisfactory.

24. Definitive information should be provided onthe levels of the individual impurities and pH throughout the shelf-life of the product.

25. Assurance should be provided that sterilising filters are tested for integrity before and after use.

26. Details should be provided on the methods by which the filling equipment is sterilised.

27. Comment should be made upon the kill rates obtained in steam sterilisation of the rubber stoppers.

28. The choice of purified water, and not water for injections BP should be justified.

29. The stability of leuprorelin acetate should be confirmed on an ongoing basis by the current assay techniques.

1.4. The company was informed of this in a letter sent on 21st April 1986 in accordance with section 21(1) of the Medicines Act 1968, and was now exercising its right to submit written representation to the committee in support of its application.

1.5. A meeting was held with the company on 16th July 1986 to discuss the section 21(1) letter.

2. ADDITIONAL DATA

3 volumes of additional data were submitted - volume 1, appendix 1 volume 1 and appendix 1 volume 2. The majority of the data relates to the chemistry and pharmacy of the product.

3. FINDINGS

3.1. The Committee considered the additional data provided by the Company and noted the recommendations of the SEAR and CPS Sub-Committees.

3.2. The Committee were reassured by the written evidence submitted by the Company in response to points 1, 2, 5-8, 10, 11, 13-26, 28 and 29 of the Section 21(1) letter.

The Committee were not reassured on points 3, 4, 9, 12 and 27.

The Committee considered that:

1. The data sheet "Warnings" section now satisfactorily emphasised the risk of "disease flare", but the evidence to justify the recommendations as to how this risk could be minimised was inadequate.
(arising from S21(1) points 3 and 4)

2. An assurance is provided that the revised specifications for the products of steps 3, 9 and 10 will be applied to every batch or part of the specification and not just for internal information. A quantitative test for impurities is included in the specification for the protected step 10 compound. (S21(1) point 9)

3. Individual limits should be included in the drug substance specification for the main impurities. (S21(1) point 12)

4. ADVICE

The Committee concluded that on grounds relating to safety and quality they would be unable to advise that a licence should be granted for this product.

5. REASONS FOR ADVICE

The Committe were not reassured as to the safety and quality of this product.

COMMERCIAL IN CONFIDENCE

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

CSM/SEAR/87/5th Meeting

BIOLS/87/2nd Meeting

ARGOS/87/5th Meeting

HEARING 2

| | |
|---|---|
| ALLPYRAL ALLERGEN EXTRACTS | PL 0055/5001 |
| CONJUVAC INJECTION | PL 0055/0051 |
| ALBAY BEE VENOM | PL 0055/0055 |
| ALBAY WASP VENOM | PL 0055/0056 |
| ALHYDROX SUSPENSION | PL 0055/0053 |

MILES, DOME/HOLLISTER-STIER
MEDICAL ASSESSOR: DR S WOOD

1. BACKGROUND

The pharmaceutical companies holding UK product licences for desensitising vaccines (Bencard, E Merck, Miles, Pharmacia, ALK) were requested in August 1986 to provide data on the efficacy and adverse reactions of their desenitising products, in order for the Committee on Safety of Medicines to conduct a review of the safety and efficacy of these products.

1.1. The data available on the licensed UK products were considered by the Committee at their meeting in September 1986. The Committee provisionally concluded that the desensitising vaccine product licences should be varied on the grounds set out in section 28(3)(g), namely that these products can no longer be regarded as ones which could safely be administered for the purposes indicated in the licences. The product licences and product particulars should be amended to include the following statements:-

a. Treatment of patients should only be carried out where full facilities for cardio-respiratory resuscitation are immediately available.

b. Special care should be taken in the treatment of patients with asthma as they may be more susceptible to severe adverse reactions.

c. Patients should be kept under medical observation for at least 2 hours after treatment.

The reason for this provisional conclusion was that there was concern regarding the possible risk of anaphylaxis in patients treated with these products.

1.2. The Chairman of the Commitee on Safety of Medicines sent a letter to all doctors and dentists on October 8th 1986 warning them of the safety hazards of desensitising vaccines and informing them of the recommendations of the CSM as above (a-c).

1.3. The pharmaceutical companies were informed of the conclusions of the CSM verbally on October 7th and in a letter sent on 14th October 1986.

1.4. The Committee published a CSM Update article in the BMJ on 11th October 1986, which discussed the efficacy and safety of desensitising vaccines and provided data on the incidence of serious adverse reactions to desensitising vaccines reported in the UK.

1.5. On 6th November 1986, Miles Laboratories accepted statements a) and b), they requested the opportunity to seek a hearing supported by additional data against statement c). The data has now been received and are placed before the Committee for their consideration.

1.6. The other pharmaceutical companies involved (Bencard, E Merck, Pharmacia, ALK) have informally agreed to accept statements a), b), and c). Applications to vary these companies' product licences have been received from Pharmacia but not from Bencard, E Merck and ALK.

2. ADDITIONAL DATA

One volume of additional written data had been received from Miles in support of their hearing.

3. DISCUSSION

3.1. Professor Collee declared an indirect non-specific interest which did not debar him from speaking. Professor Langman declared a direct specific interest and did not take part in the discussion.

3.2. The Companies had decided to pull out of the scheduled hearing at the last moment, the additional written data was therefore presented before the Committee for their consideration.

4. FINDINGS

4.1. The Committee considered the additional data and were not reassured by the evidence presented therein. The Committee therefore endorsed the recommendations of the SEAR and Biologicals Sub-Committee and concluded that the desensitising vaccine product licences should be varied on the grounds set out in section 28(3)(g), namely that these products can no longer be regarded as ones which could safely be administered for the purposes indicated in the licences.

4.2. The Committee therefore decided that product licences and product particulars of all desensitising vaccines should be amended to include the following statement:

a. Treatment of patients should only be carried out where full facilities for cardio-respiratory resuscitation are immediately available.

b. Special care should be taken in the treatment of patients with asthma as they may be more susceptible to severe adverse reactions.

c. Patients should be kept under medical observation for at least 2 hours after treatment.

5. ADVICE

The Committee decided to advise the Licensing Authority that product licences and product particulars should be amended as stated in the findings above.

6. REASONS FOR ADVICE

6.1. The Committee concluded that there was concern regarding the possible risk of anaphylaxis in patients treated with these products.

6.2. The Committee would be reassured as to the safety of these products provided that the product licences and product particulars were amended as stated in the findings.

COMMERCIAL IN CONFIDENCE
NOT FOR PUBLICATION
COMMITTEE ON SAFETY OF MEDICINES

CSM/87/5th Meeting
ANNEX D

DRAFT ENTRY IN CSM MINUTES FOR 28 MAY 1987 ON POST-MARKETING SURVEILLANCE

1. The Committee considered Tabled Paper 1, 'Post Marketing Surveillance - A Review', written by Professors Rawlins and Breckenridge.

2. Professor Asscher expressed concern about the potential for splintering on post marketing surveillance (PMS) as the Drug Safety Research Unit (DSRU), several market research firms, the Centre for Medicines Research an individual pharmaceutical companies all attempted to set up new initiatives, including massive expenditure on computers for general medical practitioners. The CSM had a statutory responsibility for monitoring adverse reactions, but was vulnerable because additional information was needed to validate hypotheses generated by yellow cards. He suggested that the Committee should take a lead in setting up an umbrella group which could advise on PMS methods and responsibilities and perhaps run PMS schemes directly.

3. Professor Rawlins said the best method of generating observational cohorts was from prescription capture. Patients should be identified as soon as possible after prescribing or dispensing: new developments in pharmacy computers and 'smart cards' would help. He did not believe companies should conduct PMS directly, not least because they could not use comparator drugs as controls; nor was CSM itself able to set up the necessary machinery directly. CSM could, though, play a key role as a catalyst in methodological developments, including links with those concerned with information technology in the family practitioner services. Professor Breckenridge stressed the urgency of CSM taking an active role, given the rapid movements of GP computing and the proposed Red Alert. He had already sounded out the President of the Royal College of Genral Practitioners, who was interested in a central initiative.

4. Dr Mann reported on informal discussions with the pharmaceutical industry which showed that the recommendation in the second report of the CSM's Adverse Reactions Working Party (ARWP) that there should be PMS on all new drugs intended for widespread long term use had created some confusion, and an expectation that £1-3m would have to be spent per study for up to 20 drugs a year. Industry would welcome a CSM lead, in liaison with the ABPI, DSRU, BMA and other medical bodies, to channel resources sensibly for example into a new initiative on prescription capture.

5. There was some discussion of the ARWP's recommendation on PMS for new drugs. The Working Party had expected that Prescription Event Monitoring (PEM) would be the main methodology. The report had been deliberately imprecise since drugs varied. The Working Party had considered it best to let industry evolve PMS methods for a few years within broad guidelines, and then review the results. Other members commented on the defects of PEM as a methodology: 1. limited numbers, delays in receiving prescriptions and starting surveillance, lack of good control group, the isolated status of the DSRU and weaknesses in its statistical analysis. It seemed that the industry did not think PEM studies alone sufficient to satisfy the ARWP's recommendation. The proposed Red Alert scheme improved on PEM in certain respects in that delay in contacting the prescriber was reduced. Conflict and confusion with the yellow card would be

minimised if the DSRU acted as CSM's 'Special Monitoring Centre' in sending out yellow cards to prescribers, and this would reduce the risk of double counting and duplicate follow-up. There would still be potential confusion between the DSRU and Regional Monitoring Centres, and a risk of 'Red alert yellow cards' being used to report reactions to other drugs. The Committee supported the Chairman's plan to meet Sir Douglas Black and Professor Inman and try to scotch the proposal altogether.

6. Other methods of PMS were discussed. Case control studies and record linkage were also important, and it would be unfortunate if large sums were spent on cohort studies to the exclusion of other valuable research. DHSS already contributed to the Medicines Evaluation and Monitoring Organisation (MEMO) at Tayside, but more funds were needed. GP computers, if widespread, might lead to a form of record linkage, but this development would be slow to reach the national coverage of PEM. It would also be some time before smart (on which Mr Grimshaw provided further information) and pharmacy computer links were in use as a national system, but it was important for CSM to play a part in pilot trials at an early stage.

7. The Committee considered that more thought was needed before an approach was made to the Royal Colleges and other bodies. It was important to be clear about the objectives of a new PMS initiative, including the quality and value of the data to be obtained and the feasibility and timescale of the methodology proposed. There was agreement that the Committee should defend its own ADR monitoring system and establish its own pre-eminent role, but concern that a new umbrella group would be out of the CSM's control particularly if funded by the industry.

8. The Committee set up a working group, with the following terms of reference:

> To consider the role of the CSM and other bodies in post marketing surveillance, including as assessment of current and developing initiatives and methodologies, and to make recommendations to the Committee.

Professors Asscher, Breckenridge, Florence, Langman, Lawson, Rawkins and Vessey agreed to take part. Dr Mann would convene a meeting as soon as possible.

Signed Minutes

CSM/87/6thMeeting

NOT FOR PUBLICATION
COMMERCIAL IN CONFIDENCE
COMMITTEE ON SAFETY OF MEDICINES

Minutes of the Zinnat Hearing held on 27 May 1987, incorporating members' amendments.

ANNEX C

CSM/SEAR/87/5th Meeting

COMMERCIAL IN CONFIDENCE

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

ZINNAT TABLETS 125mg and 250mg

PL 0004/0317-8

GLAXO

HEARING 1

Active Constituent: Cefuroxime axetil

Therapeutic Class: Cephalosporin Antibiotic

Medical Assessor: Dr Nicholson

Scientific Assessor: Dr J Ritchie

Pharmaceutical Assessor: R T Clay

1. BACKGROUND

1.1 An application for Product Licences for this product was received on 16 December 1985.

1.2 The application was considered by the Committee at their meeting in April 1986. The Committee had reason to think that, on grounds relating to safety and quality, they would be unable to advise that the licences applied for should be granted.

1.3 The Committee provisionally concluded that:

1. Reassurance would be required on the safety and quality of the formulation proposed for marketing.

2. Further evidence should be provided on the incidence of pseudomembranous colitis occurring with the formulation proposed for marketing.

3. A warning that the tablets should not be crushed should be included in the Data Sheet and on product labels.

4. The preparation should be contra-indicated in children under 5 years of age.

5. The Data Sheet should be amended to the satisfaction of the Secretariat. Attention should be paid in the Data Sheet to dosage in renal failure.

6. Further details on renal toxicity in animals are required.

7. The mutagenicity studies do not conform with the guidelines for product licence applications.

Active Substance

8. Satisfactory details of the spray drying conditions and further information on the control of crystalline state should be provided.

9. The assay limit for cefuroxime sodium (key starting material) should be raised or justified.

10. The limits proposed in the active constituent specification should be tightened or justified, in particular for

i. the assay
ii. the related substances
iii. the isomer ratio, the definition of 'total isomers' in this should be clarified
iv. the water content.

11. Satisfactory details and comments on the data obtained using size exclusion chromatography should be provided.

Dosage Form

12. Further information should be supplied on process validation. The desired physical characteristics, which might be relevant to in vivo performance should be considered, in particular the effect of granule size.

13. The correlation of dissolution test results with in vivo performance should be discussed. In particular the ability of the test to discriminate between batches of differing quality should be considered.

14. Dissolution and assay limits in the finished product specification should be tightened or justified.

15. The finished product specification should include a disintegration test and a related substances test or their absence should be justified.

1.4 The Company were informed of this in a letter sent on 20 May 1986 in accordance with Section 21(1) of the Medicines Act 1968.

1.5 On 16 June 1986 the Company wrote to the Committee giving notice that they attended to take the opportunity to seek a Hearing supported by additional data.

## 2. ADDITIONAL DATA

These additional data sent under cover of the applicant's letter of 23 September 1986 were placed before the Committee for their consideration.

## 3. PRELIMINARY DISCUSSION

3.1 Professor Geddes and Professor Newton were present at this hearing to advise the Committee.

3.2 The Committee considered the additional data submitted by the Company and noted the recommendations of the SEAR and CPS Sub-Committees.

3.3 The Committee were reassured by the additional data on points 3-11 of the Section 21(1) letter and agreed that the Company should restrict their presentation to points 1, 2 and 12-15 of the letter.

4. HEARING

4.1 The Company's representatives were

Dr Ross
Dr Williams
Mr Smith
Mr Jefferies
Dr Smith
Dr Padfield
Dr Jackson (observer)

4.2 The Chairman welcomed the Company's representatives and introduced the members of the Committee. The Company had no objections to the presence of any of the officials.

4.3 The Chairman informed the Company that the Committee were reassured by the additional written data on points 3-11 of the Section 21(1) letter, and that they should restrict their presentation to points 1, 2 and 12-15 of the letter.

4.4 The Company made the following points in their presentation:

4.4.1 In respect of points 12 and 13 the Company gave an outline of the tablet manufacturing process discussing the production of active substance particles of correct size, the requirements for a film coat to the tablet because of the extreme bitter taste and the peculiar properties of the compound on contact with water. The effect of the film coat on the bioavailability of Cefuroxime axetil was discussed and the correlation of bioavailability with the in vitro film coat rupture time (FCRT) was described. They provided a comparison of the bioavailability of tablets made in development and production facilities and demonstrated that out of 300 samples only 1 gave a low result, measured by % urinary recovery. They further demonstrated that out of 65 production batches the range for the mean FCRT lay between approximately 2.5 and 8 seconds. It was stressed that although a dissolution rate test was included as an end-process control there was no correlation with an in vivo performance and it was present merely as a quality control test. The critical control for batch to batch reproducibility of the in vivo performance was the FCRT included in the finished product specification.

The points 14 and 15 were addressed and data were provided to demonstrate that after a review of the Cefuroxime content for production batches of all strengths they would be able to raise the release specification to NLT 95%. They also proposed to include in the finished product specification limits for related substances.

The Company concluded that as a result of the work described and evaluation of production batches made this far, the Cefuroxime axetil tablets are of good quality and arise from a process which is under good control.

4.4.2 In respect of the outstanding clinical issues - S21(1) points 1 and 2:

The Company described the data-base used for the analyses of adverse events/reactions associated with the new formulation, RS3. To avoid bias due to low reporting of events such as diarrhoea in Japan, 628 Japanese patients had been excluded from the analysis of less serious events. These patients had, however, been included in the analysis of the incidence of pseudomembranous colitis and Cl difficile - associated diarrhoea.

When 1,485 patients who received RS3 were compared with 331 patients who received Augmentin in the West, the incidences of all events, gastro-intestinal events and diarrhoea were quite similar; similarly, there was no difference when the incidences of drug-related events were compared.

When the incidences of events associated with the earlier formulation, RS2, were compared with those associated with RS3, incidences were slightly greater for RS3. But similar differences were noted when early studies of Augmentin were compared with current studies of Augmentin. This historical difference in incidences was due to the improved methodology now used for the assessment of adverse events.

Concerning pseudomembranous colitis and Cl difficile - associated diarrhoea; the confidence intervals for the observed cases were for colitis: 1/135,000 to 1/625 for earlier formulations and 1/83,333 to 1/385 for RS3, and for diarrhoea: 1/135,000 to 1/625 for earlier formulations and 1/8,700 to 1/290 for RS3. One instance of colitis had been associated with an outbreak of toxin-associated diarrhoea in a hospital.

The Company concluded:

1. The total adverse event profile is similar to other broad spectrum antibiotics and earlier formulations of Zinnat.

2. The incidence of diarrhoea is similar to that of Augmentin.

3. The prevalence of pseudomembranous colitis is similar to other broad spectrum antibiotics.

4.5 The Company made the following points in response to questions from the Committee:

4.5.1 a. In respect of the low bioavailability the Company considered that it was not uncommon for antibiotics to exhibit a bioavailability of LT 50% because of the destruction by β-lactamase in the gut. It was suggested that the peculiar gelling properties with water of Cefuroxime axetil led to the gelled drug not being absorbed and being secreted unchanged.

b. The Company admitted that the rate limiting step for absorption was not exactly known. They were aware that free Cefuroxime was not absorbed and that the crystalline form was poorly available. They explained again that they considered that absorption was not dissolution controlled.

c. The effect of tablet ageing on bioavailability was questioned and the Company indicated that one bioavailability study was carried out using a development batch of tablets 15-18 months old. In this study 1 subject exhibited poor bioavailability.

d. The rapidity of the FCRT was questioned and the Company confirmed that a limit of LT <15 seconds was critical. It was considered that a FCRT above 40 seconds would affect bioavailability. They discussed the sampling per batch saying that 100 tablets were tested from each coating load and that several loads constituted a batch. The limits allowed were a mean of NMT 15 seconds with NMT 5 tablets MT 40 seconds.

4.5.2 In respect of the clinical issues:

a. The Company explained their choice of comparators; cefaclor in the USA and Augmentin i the UK rather than an ampicillin ester: many patients had been treated for chest infections. In this situation they believed that comparison with a B-lactamase-resistant antibiotic such as Augmentin was a fairer and more stringent test of the efficacy of Zinnat than B-lactamase-sensitive antibiotics such as ampicillin esters.

Augmentin had been prescribed three times daily and Zinnat twice daily in the comparative trials.

b. The Company agreed that the load of antibiotic delivered to the gut was not a major factor in the development of pseudomembranous colitis. The major risk factor was the presence of Cl difficile in the gut before antibiotics were prescribed. For non-difficile diarrhoea, however, the antibiotic load was probably an important factor.

c. The Company considered the recommended dosages in children; on a weight related basis, the dosages were higher in children than in adults: what were the implications for side effects?

The Company agreed that their data in adults indicated that diarrhoea was dose-related. Other events were so rare, however, that no dose-relationship could be discerned.

d. In childhood otitis media the comparatively high dosage recommended was due to American practice. There, it was believed that otitis media was difficult to treat; high doses of antibiotics were required.

e. Tablets could not be crushed because of the foul taste. The bioavailability of bi-sected tablets was probably satisfactory, but the one foul-tasting edge would still pose a problem. An elixir was being developed for children.

4.6 Discussion by the Committee after the Hearing

Members were minded to advise the Licensing Authority to grant the licences applied for.

5. FINDINGS

The Committee were reassured by the additional data and the Company's presentation as to the safety and quality of this product.

6. ADVICE

The Committee agreed to advise the Licensing Authority to grant a product licence for this product.

7. REASONS FOR ADVICE

The Committee were reassured as to the safety and quality of the product.

GRO-C