

NOT FOR PUBLICATION

COMMERCIAL IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

SUB-COMMITTEE ON BIOLOGICAL PRODUCTS

Minutes of the meeting held on 4 January 1984

PRESENT

ALSO PRESENT

[REDACTED] (Chairman)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

} NIBSC

[REDACTED] (Pharmaceutical Assessor)

[REDACTED] (Secretary)

1. Confidentiality and Announcements

The Chairman informed the Sub-Committee that two new members had been appointed and that they were [REDACTED] and [REDACTED]. He explained that [REDACTED] was unable to attend meetings until August 1984.

The Chairman paid tribute to the work of [REDACTED] and [REDACTED] as members of the Sub-Committee. Both these members retired from CSM(B) at the end of 1983.

The Chairman reminded members that the material they received was confidential and should not be disclosed outside the meeting.

2. Apologies for Absence

Apologies for absence had been received from [REDACTED] and [REDACTED].

3. Minutes of the Meeting held on 14 September 1983

These were agreed and signed by the Chairman as a correct record of the proceedings.

4. Matters arising from the minutes

The Sub-Committee noted the CSM's advice on applications previously seen by the Sub-Committee.

5. Consideration of applications

- 5.1 PL/1317/0001-Solco Basle Ltd - Solocotrichovac
- 5.2 CT/5467/0001 - Crinos SpA - Defibrotide Injection 200mg/2.5 ml
- 5.3 CT/0015/0101 - Boehringer Ingelheim - Berofor Nasal Spray

Dr Tyrrell declared a non-specific interest in this application.

- 5.4 PL/3478/0090-95 - Warrick Pharmaceuticals Ltd - Alpha-2 Interferon

- 5.5 PL/3473/0011 - Common Services Agency - Human Immunglobulin.

The Sub-Committee's recommendations on these applications are at appendices A-E.

6. Written representation

- PL/4447/0004 - Alpha Therapeutic - Antihaemophilic Factor
(Human) Wet Paste
(Bulk) Cryoprecipitate)

The Sub-Committee's recommendation on this written representation is attached at appendix F.

7. Items for Information

MLX 149 + 149 Corrigendum, MLX 150, Statutory Instrument 1983 No 1212
MAIL 38

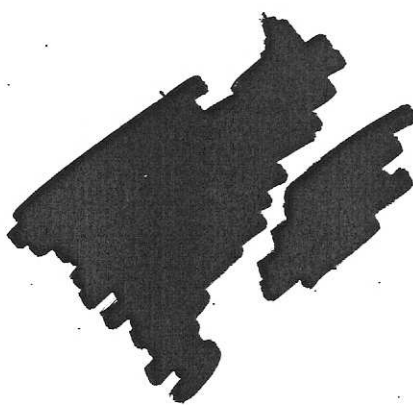
These were circulated to Members for their information

8. Any other business

The Chairman informed Members that this was [REDACTED] last attendance at CSM(B) and thanked her for her help and guidance.

9. Date and Time of next meeting

Wednesday 7 March 1984 at 10.30 am.



No

PL/1317/0001

Coy

Solco Basle Ltd

Product

Solcotrichovac

Therapeutic Class

Bacterial Vaccine

Active Constituents

Lactobacillus
acidophilus, eight
different strains:
LAT 01, 02, 03,
04, 06, 07, 08
and 11.

SUB-COMMITTEE ON BIOLOGICAL PRODUCTS 4 JANUARY 1984RECOMMENDATION

On the evidence before them the Sub-Committee recommended the grant of a Product Licence on condition that:

1. confirmation is given that the intended shelf-life of the product is three years when stored at 4° - 8°C. and this will be printed on the container,
2. the indications are limited to "Therapy and prophylaxis of Trichomonas infection in women",
3. the dosage schedule is restricted to the three dose primary course. If the Company should wish to recommend the use of subsequent doses, further evidence of safety and efficacy would be required,
4. the Batch Release procedure should apply, to include the provision of bulks and in-process samples.

REMARK

Further studies on the mode of action of the vaccine, the nature of protective antigen(s) and the effect on the vaginal flora would be helpful.

No

CT/5467/0001

Coy

Crinos SpA

ProductDefibrotide
Injection 200mg/2.5mlTherapeutic ClassAnalgesic, Fibrinolytic,
VasodilatorActive constituent

Defibrotide 200mg

SUB-COMMITTEE ON BIOLOGICAL PRODUCTS

4 JANUARY 1984

RECOMMENDATION

On the evidence before them the Sub-Committee recommended the issue of a Clinical Trial Certificate on condition that:

Drug Substance

1. Further information is provided on the extraction and purification of the raw material,
2. the specification is amended to include tests with suitable limits for:
 - i) molecular weight
 - ii) adenosine
3. additional quantitative stability data is provided,

Dosage Form

4. further information is given on the manufacture and sterilisation process,
5. batch analytical profiles are provided showing the results of all the tests in the finished product specification for several named production batches,
6. additional stability data are forwarded which shows the level of apurinic acids reached on storage,
7. satisfactory justification is given for the presence of preservatives in this single dose injectable,

Protocol

8. a satisfactory specification for the placebo is provided,
9. the monitoring of the patients will include examination for antibodies to the product and for immune complexes,
10. the batches used in the Clinical Trial meet the stated specification and samples are submitted to NIBSC.

Remark

1. By the product licence stage, objective evidence of efficacy in controlled trials would be required.

No

CT/5467/0001

Co

Crinos SpA

Product

Defibrotide
Injection 200mg/2.5ml

Therapeutic Class

Analgesic, Fibrinolytic,
Vasodilator

Active constituent

Defibrotide 200mg

2. By the product licence stage a satisfactory bio-assay should be applied to each batch unless evidence is presented on adequate characterisation by physico-chemical methods.

No

CT/0015/0101

CoyBoehringer Ingelheim
LtdProduct

Berofor Nasal Spray

Therapeutic ClassRecombinant Human
InterferonActive ConstituentRecombinant
Human Interferon
α 2SUB-COMMITTEE ON BIOLOGICAL PRODUCTS 4 JANUARY 1984RECOMMENDATION

On the evidence before them the Sub-Committee recommended the issue of a Clinical Trial Certificate on condition that:

1. the manufacturers of each phase of the product, and the testing for which they are responsible are clearly stated,
2. further satisfactory details are provided on the fermentation process, to include test methods for bacterial contamination,
3. evidence of the integrity of the plasmid at the end of fermentation cycles is provided,
4. justification is provided for the use of polyethylenimine in the extraction process together with evidence of the absence of its monomer from the product,
5. further information is provided on the characteristics and purity of the monoclonal antibody used in the process, together with data on the possible contamination of the product with the antibody and related materials,
6. information is provided on the biological activity of this variant interferon molecule,
7. further information is provided on the tests to be undertaken on the patients; these should include lung function tests and immunological monitoring,
8. hypersensitivity to penicillin is a contra-indication to the use of the product,
9. samples of the plasmid, in process materials and final product are made available to NIBSC.

No

PL/3478/0090-95

CoyWarrick Pharmaceuticals
LtdProductTo be decided
(α -2 Interferon)Therapeutic Classanti-viral/
anti-cancer agentActive constituent α 2 InterferonSUB-COMMITTEE ON BIOLOGICAL PRODUCTS 4 JANUARY 1984RECOMMENDATION

On the evidence before them the Sub-Committee, on grounds of safety, efficacy and quality, were unable to recommend the grant of a Product Licence for this product.

The Sub-Committee considered that:

1. evidence of the integrity of the plasmid (restriction enzyme mapping) at the end of the fermentation runs should be provided,
2. evidence should be presented of the capacity of the purification method to remove E.Coli proteins,
3. the total impurities should be limited to 2% and evidence on the nature of the impurities should be provided,
4. electrophoretic evidence of impurity profiles for each batch should be provided on good quality photographs,
5. contaminated fermentation batches should not be used for further processing,
6. inadequate evidence of efficacy had been presented,
7. clinical data should include the results of careful monitoring for the development of immunological reactivity especially to interferon,
8. the Batch Release procedure should apply to include the provision of samples of the plasmid, bulks, in process materials and the house standard.

No

PL/3473/0011

Coy Committee of
Management, Scottish
Health Service,

Common Service Agency

Product

Human Immunoglobulin

Therapeutic Class

Blood Product

Active Constituent

Human Immunoglobulin

SUB-COMMITTEE ON BIOLOGICAL PRODUCTS 4 JANUARY 1984RECOMMENDATION

On the evidence before them the Sub-Committee, on grounds of safety, quality and efficacy, were unable to recommend the grant of a Product Licence for this product.

The Sub-Committee considered that:

1. clarification should be provided on certain aspects of the manufacturing process,
2. the evidence of safety from studies in volunteers and patients was insufficient,
3. the evidence of efficacy in the treatment of primary hypogammaglobulinaemia by intravenous infusion was insufficient,
4. there was no evidence presented concerning the wide range of other uses and routes of administration proposed,
5. evidence for the presence of antibodies to common pathogens was insufficient,
6. consideration should be given to the possibility that the porcine pepsin in the product may be antigenic in man.

REMARK

In the event of a Product Licence being granted:

- 1) on-going stability data should be provided;
- 2) the Batch Release procedure should apply to include the provision of bulks and in-process samples.

No

PL/4447/0004

CoAlpha Therapeutic
CorporationProductAntihaemophilic Factor
(Human)Wet Paste (Bulk
Cryoprecipitate)Therapeutic Class

Blood Product

Active Constituent

Human Factor VIII

Sub-Committee on Biological Products 4 January 1984

RECOMMENDATION ON WRITTEN REPRESENTATION

The Sub-Committee considered the additional data supplied by the Company in support of their written representation against the CSM's provisional conclusion but they were unable to recommend the grant of a Product Licence for this product.

The Sub-Committee considered that:

1. the Company were unable to confirm that the bulk cryoprecipitate would be prepared by Alpha Therapeutic only from source plasma (Human) derived from their own licensed plasmapheresis centres and their arguments for an alternative arrangement were not accepted (point 1 of the Section 21(1) letter),
2. satisfactory evidence had not been provided to show that the cryoprecipitate is at least equivalent in quality to that used for the manufacture of Alpha Therapeutic's US licensed factor VIII (point 2 of the Section 21(1) letter),
3. the information presented on the control of the material during transport to the UK was inadequate (point 3 of the Section 21(1) letter),
4. a satisfactory undertaking had been provided, by the Company, to supply donor lists to the manufacturer of any finished dosage form (point 4 of the Section 21(1) letter),
5. in the event of a licence being granted for this product, the batch release procedure should apply, to include the provision of protocols and samples of bulks as required. The Sub-Committee did not accept the Company's argument that the batch release procedure should not apply (point 5 of the Section 21(1) letter),
6. satisfactory details of the manufacturing process had been provided (point 6 of the Section 21(1) letter).

Therefore points 1, 2, 3 and 5 of the Section 21(1) letter remained outstanding.