NOT FOR PUBLICATION

CSM/BIOLS/92/4th MEETING

COMMITTEE ON SAFETY OF MEDICINES

SUB-COMMITTEE ON BIOLOGICALS

Minutes of the meeting starting at 10.30am, on Wednesday 7th October 1992, in the 19th Floor Conference Market Towers.

Present

MEMBERS

Dr D A J Tyrrell (Chairman)
Professor J Melling
Dr P Minor
Dr G C Schild
Professor R S Tedder

GUEST MEMBER

Dr R Thorpe

COMMITTEE SECRETARIAT

Dr J Purves (Principal Assessor)
Mr E Hazell (Secretary)
Mrs M Dow
Dr E Gate
Dr F Rotblat
Dr A Thomas
Dr L Tsang
Mrs J Tufnell

Observers

Professor H S Jacobs

Also Present

Dr M Kavanagh
Mrs A Oatley

1. APOLOGIES AND ANNOUNCEMENTS

1.1 The Chairman reminded the Sub-Committee that the papers and proceedings were confidential and should not be disclosed. Members were also reminded to declare their personal specific, personal non-specific, non-personal specific and non-personal non-specific interests in all agenda items.

1.2 Apologies had been received from Professors Banatvala and Gull also Drs Gingold and Jeffcoate for the day and from Professor Jacobs for the afternoon.

1.3 The Chairman welcomed Dr Thorpe from the NIBSC who attended as member for the day and Professor Jacobs who attended as an observer from the CSM.

2. MINUTES OF THE MEETING OF 8th JULY 1992

2.1 The Chairman signed the minutes as a true record of the meeting.

GRO-C: A J Tyrrell

3. MATTERS ARISING FROM THE MINUTES

None

4. WRITTEN REPRESENTATION

The Sub-Committee considered application for the following product.

4.1 PL 04913/0003: Zyplast Collagen Implant: Collagen (UK)

The recommendation is at Appendix A1

5. HEARINGS

The Sub-Committee considered applications for the following products.

5.1 PL 00337/0167: Alferon N: Napp Laboratories

Professor Tedder declared a non-personal non-specific interest, but this did not debar him from taking part in the decision

5.2 PL 10673/0001-3: Octavi 250, 500 & 100IU: Octapharma

The Sub-Committee noted Tabled Paper II.

The Company had provided information on a number of viral inactivation studies performed over several years.

Some studies showed good results whilst others were inconclusive and difficult to interpret; some had been performed before the CPMP Guidelines on Viral Inactivation Studies were available.

The Sub-Committee considered that it could be criticised for selecting only the good results in coming to a decision and agreed that the Company should be asked to provide further assurance of the validity of their studies and the virological safety of the product.

The recommendations are at Appendix B1 to B2

6. NEW PRODUCTS

The Sub-Committee considered applications for the following products, their recommendations are at Appendix C1 to C3

6.1 CPMP 00086/0152-3: Berileukin: Injection Hoechst/ Beringwerke

Professor Melling declared a non-personal non-specific interest, but this did not debar him from taking part in the decision

6.2 CPMP 00057/0338: Pfizer E5 Mouse Monoclonal Antibody: Pfizer (UK)

Professor Melling declared a non-personal non-specific interest, but this did not debar him from taking part in the decision

6.3 CPMP 12375/0001-2:Ceredase: Genzyme BV

Professor Melling declared a non-personal non-specific interest, but this did not debar him from taking part in the decision

7. PAPER

7.1 Anti-HCV testing of donations used in the manufacture of blood products

The sub-committee endorsed Tabled Paper I provided that:-

a. In point 3 "placed on the market" is replaced by "released for sale or otherwise released for human use"; and

b. Group 3 are considered on a case by case basis; and

7.2 CPMP Products - Written consultation on: Clivarine Injection - CPMP 000169/0034; and Granocyte - CPMP 12054/0001

Committee members attention was drawn to the recommendations for two products processed by written consultation.

Dr Purves thanked committee members for the successful way in which this procedure had functioned with their assistance. Some members expressed, however, that they would prefer an opportunity to discuss applications at Committee. This was noted Dr Purves stated that the use of the written procedure would be less next year, since the much Sub-Committee would have the opportunity to meet on a greater (6) number of occasions.

8. ANY OTHER BUSINESS

Dr Purves thanked the Chairman and Sub-Committee members for their work over the last three years, the Chairman then thanked the Secretariat for their support.

9. DATE AND TIME OF NEXT MEETING

Wednesday 13th January 1993 at 10.30am.

A1.

COMMERCIAL IN CONFIDENCE

NOT FOR PUBLICATION

COMMITTEE ON DENTAL AND SURGICAL MATERIALS

SUB-COMMITTEE ON BIOLOGICALS

SUB-COMMITTEE ON CHEMISTRY, PHARMACY AND STANDARDS

Meeting : NOVEMBER 1992

PL Number : PL 4913/0003

Company : Collagen (UK) Ltd

Product : Zyplast Collagen Implant

Pharmaceutical Assessor: Dr A H Thomas

Medical Assessor : Dr S Eisen

WRITTEN REPRESENTATION

This application was considered by the Committee on Dental and Surgical Materials at their meeting in March 1989. The Committee were minded to advise that a product licence should be refused unless certain conditions were followed.

BIOLOGICALS RECOMMENDATION

On the further evidence before them, the Sub Committee were unable to recommend the grant of a Product Licence.

The Sub-Committee considered that:

1. Viral inactivation studies should have been provided to demonstrate that non-enveloped viruses are inactivated by the process for manufacturing the collagen solution (Zygen). (Arises from Point 7.1 of the Section 21.1 letter.)

The Sub-Committee were satisfied with the replies to Points 4, 6, 8-10.

B1

CSM 92/11 MEETING
BIOLS 92/3RD MEETING

COMMERCIAL IN CONFIDENCE

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

SUB-COMMITTEE ON BIOLOGICALS

MEETING	:	7 OCTOBER 1992
PL NUMBER	:	0337/0167
PRODUCT	:	ALFERON N
PHARMACEUTICAL ASSESSOR	:	J TUFNELL

Hearing

The application was considered by the Sub-Committee on Biologicals at its meeting in July 1991 and by the Committee on Safety of Medicines at its meeting in September 1991. The CSM had reason to think on grounds relating safety and quality they might be unable to advise the grant of a licence.

BIOLS RECOMMENDATIONS

On the further evidence before them the Sub-Committee are unable to recommend the grant of a product licence.

The following points are considered to have been cleared.

3, 4.6, 4.8, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 6.2, 6.4, 6.6, 6.7, 6.8, 6.10, 6.11, 7.1, 7.2, 7.3, 8.3, 10.1.2, 10.1.3, 10.1.7, 10.1.8, 10.3, 10.4, 12.1, 12.2.1, 12.2.2, 12.3.1, 12.3.3, 12.3.4, 12.5, 13, 14, 15.

The following points remain as a result of incomplete responses to some questions.

B/cont.

MAJOR POINTS

1. Virology

1.1 The viral validation studies are not acceptable. A range of viral probes should have been used. The Company are reminded that Guidance on Validation of Viral Clearance is available from the CPMP.

1.2 The methods of analysis used to screening source leukocytes for contamination should have been validated. Every batch of source leukocytes used to produce Alferon N should be screened by these test.

1.3 The potential riak of viral contamination arising from the NK-2 should have been addressed.

1.4 The removal of virus during regeneration that is retained from the product by the affinity column, should have been demonstrated.

(Arises from questions 1, 6.9)

2. Product Consistency

2.1 The traces provided of RP-HPLC analysis show the product is multicomponent. The consistency of the product from batch to batch in terms of content of each component should have been demonstrated and related to clinical trial batches.

2.2 The RP-HPLC method should have been validated.

(Arises from questions10.2)

3. Potency Assay

3.1 Full validation of the Potency assay method (CPE) should have been provided including evidence that the method is capable of detecting degradation of the product.

3.2 Results of CPE assay should have been provided. The mean potency of several batches should be stated.

3.3 Fiducial limits should have been provided for the potency assay.

(Arises from questions 10.1.1, 10.2, 12.1, 12.2 and 12.4)

B1 cont

POINTS FOR CLARIFICATION

4. Source Materials derived from blood or plasma

4.1 The donors of source leukocytes used to product Alferon N should be tested for absence of HIV-2 using an appropriate test method.

(Arises from question 4.1)

4.2 The donation sites for the serum and the method of manufacture for Agamma Human Serum should have been provided. This may be provided on a Commercial in Confidence basis from NABI.

(Arises from question 4.2 and 4.3)

4.3 The acidification process used to remove contamination from the induction Primer (Crude Natural Interferon) should have been validated. Details of the source and manufacture of this Primer should have been provided (arises from question 4.4).

5. Source Materials of Other Origin

5.1 Clarification should have been provided of which constituents of MEM comply with BP/EP specifications (arises from question 4.7).

5.2 The specific source of bovines used to provide the Bovine Serum Albumin should have been provided. Evidence of compliance with CSM guidelines on BSE should have been provided (arises from question 5.1).

6. Manufacture

6.1 The in-process control limits and methods applied to induction should have been provided (arises from question 4.5).

6.2 As the harvest may be stored for up to 7 days at 2-8°c, in-process controls to ensure the absence of contamination at the end of this storage time should have been applied prior to further processing (arises from question 6.1).

7. Purification

7.1 Details of the selection of the hybridoma from which the murine IgG, NK2, is produced. Details of the coupling procedure for NK2 to Sepharose 4B the stability and demonstration of specificity of the bound NK2 should have been included.

(Arises from question 6.3).

7.2 Data should have been provided to support the proposed maximum reusage for the affinity column including validation. The Clearance for virus retained on the column from the product by the regeneration process should have been validated. The levels of leaching of NK2 from the column into the product as the column ages should have been investigated (arises from question 6.5).

8. Impurities

8.1 The non-interferon proteins seen on SDS-PAGE should have been identified especially if they are not of human origin (arising from question 8.2 and 12.2.4).

9. Active Ingredient Specifications

9.1 An ovine antibody is used as the identity test for the active ingredient. The consistency and purity of the antigen that is used to produce the ovine polyclonal antibody should have been demonstrated (arising from question 8.1).

9.2 In light of the Batch Analysis results provided the limits for murine IgG, residual DNA and content of other proteins in the Active Ingredient specification should be tightened. The ELISA method for detecting residual NK2 in the product and the DNA hybridisation method should have been fully validated. The purity and consistency of the rabbit anti-human albumin IgG should have been demonstrated (arising from question 9, 10.2, 10.14, 10.1.5, 10.16, 12.3.2).

10 Dosage Form Specification

10.1 In light of the batch analysis results provided the limits for endotoxin and % neutralisation in the product specification should be tightened (arising from question 12.2).

10.2 In the specification for the product the BP/EP Sterility Test and LAL Test methods should be used. (Arises from question 12.4).

11. Dosage Form Shelf Life and Stability Data

11.1 In the stability studies evidence of degradation was demonstrated by SDS-PAGE. The absence of SDS-PAGE in the product specification should be justified (arising from question 16).

11.2 The proposed storage conditions and in-use shelf life for the finished product should have been stated and been supported by stability data. A single vial of product must only be used for one patient (arises from question 11).

B2.

COMMERCIAL IN CONFIDENCE

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

SUB-COMMITTEE ON BIOLOGICALS

MEETING	:	7 October 1992
PRODUCT LICENCE NUMBER	:	10673/0001-3
COMPANY	:	Octapharma Limited
PRODUCT	:	Octavi 250, 500, 1000IU
PHARMACEUTICAL ASSESSOR	:	Mrs M Dow

HEARING

This application was considered by the Committee on Safety of Medicines at their meeting in January 1992.

The Committee had reason to think that on grounds relating to quality and quality in relation to safety they would be unable to advise that the product licence applied for should be granted.

The Sub-Committee then considered the additional evidence provided by the Company and were satisfied by the replies to points 4, 5, 10, 12, 14, 16, 18, 19.1, 19.2, 19.3, 19.4 and 19.5 of the Section 21(1) letter.

BIOLOGICALS SUB-COMMITTEE RECOMMENDATION

The Sub-Committee were unable to recommend that a product licence should be granted. The Sub-Committee considered that:

1. Results of viral inactivation studies were inconsistent.

2. Assurances should be provided that all collecting bags will comply with the Ph Eur if tested. Storage conditions for filled bags should be clarified and justified. (Ref point 7 of the S21(1) letter.)

3. Assurances should be provided that all anticoagulant solutions will comply with the Ph Eur if tested. (Ref point 8.)

B2 cont

4. Plasma screening methods should be investigated in the event of a donor becoming sero-positive. (Ref point 6.)

5. Storage temperatures for plasma and cryoprecipitate at the Octapharma plant should be justified. (Ref point 9.)

6. The ethanol used in the extraction process should be fully characterised with respect to impurity content. (Ref point 13.)

7. **Virus inactivation**

7.1 Full justification should be provided for the absence of in-process control limits for solvent/detergent.

7.2 Justification should be provided for the variation in solvent/detergent contact times. The effect of the maximum contact time on the stability of the product should be demonstrated. (Ref point 15.)

7.3 **Studies** (Ref point 16.)

7.3.1 Virus titres should be provided for all positive control samples at the beginning and end of studies.

7.3.2 The methods used to interrupt the viral inactivation process(es) should be fully described and adequately validated.

7.3.3 **HIV-1 Kinetic study**

Full information should be provided for the methodology and control samples.

8. Labels should comply with the requirements of the BP for Dried Factor VIII Fraction.

9. The shelf-life at room temperature should be defined and justified.

10. Discrepancies in potency assay results identified by NIBSC and resulting in over-labelling should be addressed satisfactorily.

Remark to the Company

1. This product and plasma pools will be subject to a batch release procedure. As well as samples of product and pools it will be necessary to include quality assurance and performance evaluation information for the kits used in screening.

2. The Water for Injection diluent should be the subject of a separate product licence application.

COMMERCIAL IN CONFIDENCE

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CSM/BIOLS/CPS

APPENDIX C1

COMMITTEE ON THE SAFETY OF MEDICINES

SUBCOMMITTEE ON BIOLOGICALS

Meeting	: October 1992
PL Number	: CPMP PL/00086/0152-3 (Concertation No 37)
Company	: Hoechst
Product	: Berileukin Injection (Ex Prokine Inj)
Pharmaceutical Assessor	: Dr E N Gate
Preclinical Assessor	: Dr R Lee
Medical Assessor	: Dr F Rotblat

CPMP CONCERTATION - 2nd PHARMACEUTICAL CONSIDERATION

An application for a marketing authorisation for Berileukin (Ex Prokine) was submitted as a Biotech application to the Rapporteur in November 1991. The application was considered by CSM in February 1992. The rapporteur's assessment report was circulated to member states on 28 February 1992. Comments on the assessment report were requested by 1 May 1992. The Company were sent a consolidated list of questions on 29 May 1992.

RECOMMENDATIONS

On the further evidence before them, the subcommittee recommended that the following points should form part of the Rapporteur's assessment report:

(points marked * are common to Biologicals and CPS)

PART I

SUMMARY OF PRODUCT CHARACTERISTICS

1. The proposed statement in the SPC regarding the differences between native human GM-CSF and the active ingredient in Berileukin is acceptable. However, it would be useful if an updated SPC could be provided. (point for clarification)

L1 cont.

PART II

SPECIFIC ACTIVITY/UNITAGE/BIOASSAY

2. There is concern about assay design, standardisation and analysis. (major point)

2.1 The unitage appears to have been presented in a confusing way in the documentation and it appears that different unitages have been used; for example for a 500ug vial, the unitage is given as 8.5 x 10E7 U (data, August 1992 01 pp 3[Q3], 74 [Q63]) and as 2.5 x 10E7 (data August 1992, 01 p74 [Q63]). The specific activity should be clearly indicated.

2.2 The unitage should be that of candidate WHO international standard 88/646 or the international standard when established.

2.3 The bioassay should be adequately designed, statistically analysed and validated in line with Ph.Eur requirements for bioassays. Unless justified, a parallel line assay should be used.

2.4 The rationale for having different limits for the bioassay in the drug substance and dosage form specifications should be given and justified. Limits should be tightened significantly and should be supported by batch analyses. Appropriate limits for mean result and fiducial limits still need to be applied. The proposal for limits of mean result ± 2, 2.5 or 3 standard deviations seems arbitrary.

PART IIB

3. The maximum time for preparation, holding and filling of the bulk solution in dosage form manufacture should be indicated. (point for clarification) *

PART IIC

GENETICS

4. The Company have provided information on plasmid copy number using a different plasmid than that used for Berileukin and it was unclear whether the media used were the same as that used for Berileukin. An assurance should be given that the plasmid stability will be confirmed from data on the plasmid copy number after a fermentation using the plasmid and manufacturing conditions utilised for Berileukin. (point for clarification)

5. The Company should consider investigating other methods in order to detect single point mutations in the plasmid. eg, single strand conformation polymorphism, or by investigating "loss of function" mutations in the selectable marker gene (Tryp) on the plasmid. (remark)

FERMENTATION

6. The Company should investigate their fermentation process to ascertain at what stages of fermentation sargramostim is produced, whether different glycoforms are produced at different stages and, on glucose utilisation. It should be clarified whether the 'degree' of disulphide bond formation varies between glycoforms and whether the degree of disulphide bond formation affects the degree of glycosylation. This information could be provided on an on-going basis. (point for clarification) *

PURIFICATION

7. The protein loading used for columns should be indicated. (point for clarification) *

8. The effect of reprocessing on the quality of the drug substance (e.g. impurity levels, distribution of glycoforms, levels of clipped species, potency etc) should be discussed and justified. (point for clarification) *

9. RP-HPLC eluates stored at 2-8°C for prolonged periods (eg more than a few days) should be monitored for microbial contamination. (point for clarification) *

DRUG SUBSTANCE

10. The Company's response to Q56 does not really resolve the situation as to whether the three lower molecular weight glycoforms ('15.5, 16.8, and 19.8KD') have the same biological activities. In view of this, (unless further justified) the Company should not claim that the three species have exactly the same biological activities. (point for clarification)

DRUG SUBSTANCE SPECIFICATIONS

11. It is proposed that the acceptance criteria for the RP-HPLC will include a statement that the test sample must be comparable to the reference standard. It would be helpful if a copy of the elution profile for the reference standard could be provided (with column loading indicated) with the updated specifications. (point for clarification) *

12. The proposed limit of 11% for the hyperglycosylated species has not been justified. The limit should be reduced significantly. (major point) *

13. Further recent batch data should be presented to support the limits proposed in the drug substance specifications. The proposal of allowing limits of the mean ± 2.5SD or 3SD seems arbitrary. (point for clarification) *

-1 cont

14. It should be clarified whether the proposed acceptance criteria fc the peptide mapping test would exclude batches in which new peak were observed in the map. The presence of a new peak might sugges that the integrity or purity of the drug substance was in doubt. (point for clarification) *

TRANSPORTATION OF PURIFIED DRUG CONCENTRATE

15. There is still concern that storage at 2-8°C for 30 days of the purified drug concentrate could compromise the quality of the drug substance if microbial contamination was to occur. Q101 (of list of May 1992) remains - If the purified drug concentrate (a protein solution) is going to be stored for prolonged periods in the liquid state then it should be sterile. (point for clarification) *

PART IIE

FINISHED PRODUCT SPECIFICATIONS

16. In the specifications many acceptance criteria as given as 'comparable to reference standard' or similar statement. It would be helpful if copies of gels, chromatograms etc of the reference material could be provided with the updated specifications. (point for clarification) *

17. Batch analysis data should be presented to support the proposed limit for protein determination in the finished product specifications. (point for clarification) *

18. The proposed limit of 11% for the hyperglycosylated species has not been justified. The limit should be reduced significantly. (major point) *

PART IIF

STABILITY

19. Updated stability results for the drug substance should be presented. (point for clarification) *

20. In response to Q119 (of list of May 1992) the Company argue that oxidised GM-CSF variants would be detected by the peptide mapping test. However, it is unclear what the likely limit of detection of the peptide mapping test would be for oxidised GM-CSF variants. An assurance should be given that stability studies will investigate using appropriate methods the potential presence of GM-CSF variants including oxidised forms. (point for clarification) *

21. Unless justified, a limit for peak 1A (seen in method T-075) should be introduced into the specifications. (point for clarification) *

PART V

22. Acceptability of labelling is subject to national approval. However, core information (eg name, expression of strength etc) should be in - line with the SPC. (remark) *

CI cont.

23. Testing on importation: It appears that Gel filtration is not yet part of the finished product specifications. In addition the method reference number for the Western Blotting test is different to that stated in the finished product specifications. The QC site for testing on importation should be indicated. (point for clarification) *

C2.

CSM 92/11th MEETING
BIOLS 92/3RD MEETING

COMMERCIAL IN CONFIDENCE

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

SUB-COMMITTEE ON BIOLOGICALS

MEETING	:	7 OCTOBER 1992
PL NUMBER	:	00057/0338
COMPANY	:	PFIZER
PRODUCT	:	PFIZER E5
PHARMACEUTICAL ASSESSOR	:	J TUFNELL

RESPONSE TO CPMP REASONED OBJECTIONS

The application was considered by the Sub-Committee on Biologicals at its meeting in May 1990 and by the Committee on Safety of Medicines at its meeting in July 1990.

The CSM raised reasoned objections which were forwarded to the CPMP relating to safety, efficacy and quality.

BIOLS RECOMMENDATION

On the further evidence before them the Sub-Committee considers the reasoned objections have not been satisfactory resolved and the outstanding objections should be forwarded to the CPMP for consideration.

The outstanding Reasoned Objections are as follows:-

(These include CSM questions 3, 5, 39, 42, 43, 46, 53, 56, 58, 66, 88, 90, 96, 98, 103, 107, 112)

16

C2 cont

MAJOR POINTS

Method of Manufacture

1. The method of manufacture is likely to result in a starting material with viral contamination. The purification process has not been adequately demonstrated to be capable of inactivating a range of viral probes. (Arises from question 32, 43, 44, 66, 67, 68, 69, 71, 72, 73, 74).

2. The likely level (and type) of viral contamination in the starting material determined should be justified (arises from questions 32, 34, 50, 70).

3. As each batch is from a different selection of mice each batch will need to be tested for viral contamination.

4. The current proposed scale of purification should be validated and the proposed operating conditions for the columns should be clearly defined (arises from questions 53, 58, 66, 67, 68, 69).

5. The maximum permissible number of regenerations and reusages of the purification columns should be clearly stated. This level of reusage should be validated in terms of product consistency and viral clearance. Adequate in-process control should be applied to ensure product consistency as columns age. (Arises from questions 56, 80).

6. Reprocessing of the product during purification is not acceptable (Arises from questions 11, 57).

Specifications

Active Ingredient

7. The proposed specification for the active ingredient is not acceptable. Based on the batch analysis and stability results presented, the limits for unknown proteins, aggregates and fragments should be tightened or be justified.

The proposed limits for "potency" and content of fragments should be justified by clinical or other data.

The absence of controls for carbohydrate content should be justified. (Arising from questions 7, 95, 96.1, 96.2, 96.4, 96.6).

Bioassay

8. The Company should continue to develop a Bioassay which relates in vitro activity to in vivo potency (arising from questions 5, 98.10, 96.8).

C2 cont.

Potency Assay

9. The % binding assay presented as the control of "potency" is unacceptable.

9.1 The % binding assay does not reflect the invivo potency of the product. The increase in % binding as the product degrades is not likely to be reflected by the clinical experience.

9.2 The details of the assay method were inadequate. It is unclear what are the parameters of the methodology critical to the % binding value obtained. The reproducability of the method has not been demonstrated.

9.3 The purity and consistency of the proposed substrate has not been demonstrated.

9.4 Full information should be provided of the data used to generate the graph (provided in response to question 98.11) to demonstrate the relationship between "% binding" and content of fragments (arising from questions 6, 88, 89, 91, 98.8, 98.11, 112).

10. Dosage Form Specification

As the product preciptates on storage the specification for the dosage form should contain a limit for precipitated protein which is justified by stability data.

The proposed limits for content of unknown protein, and aggregates should be tightened or justified

The proposed limits for % binding and content of fragments should be justified by clinical data.

The variability in % binding between the active ingredient and dosage form prepared from the same batch of material should be discussed eg batch EM810831 with a potency of 114% as active ingredient but 88% in the dosage form (arising from question 107).

11. Stability and Shelf Life Active Ingredient

Based on the stability data presented, the proposed shelf life of 27 months at -10 to -20°C for the active ingredient is not justified.

12. Dosage Form

12.1 The proposed limits for content of fragments and the % binding limits need further justification before the shelf life of 15 months for the dosage form at 2-8°c can be approved.

12.2 The extent of protein precipitation on storage of the dosage form should be established before a shelf life for the dosage form can be proposed.

C2 cont.

12.3 The potency of aged product, after filtration to remove the preciptated protein, should be demonstrated by stability data (arising from questions 3, 107.4, 108, 114, 107, 115).

Reference Standard

13 The Reference Standard characterisation should include the content of aggregates. The standard used for the % binding assay should be stated (arising from question 103).

MINOR POINTS

14. The Company should confim it will apply to the CPMP for any future changes to the growth media for the Working Cell Bank (arising from question 39).

14. Confirmation is required that all sterilsing filters are integrity tested before and after use including those used for sterilisation of buffers (arising from question 42).

15. All materials used in production should comply with the European Pharmacopoeia specifications where such exist (arising from questsion 46).

J TUFNELL
SEPTEMBER 1992

CPS

Date: October 1992 CSM/BIOLS/SEAR 9th Meeting Appendix C3

Number:

CPMP 12375/0001-2

Company:

Genzyme BV

Product:

Ceredase 50IU & 400IU

Therapeutic Class:

Enzyme

Active Constituent:

Aglucerase

SUB-COMMITTEE ON BIOLOGICALS

RECOMMENDATION

On the evidence before them, the Sub-Committee, recommended the following comments be forwarded to the CPMP:

PART II A

1. Development Pharmaceutics

1.1 In view of the instability of the "400IU" formulation, optimisation of the proposed formulation should be addressed with particular reference to the ratio of human serum albumin to aglucerase in the finished product.

1.2 It is noted that an in-line particulate filter is recommended for the administration of this product. The issue of adsorption and the effect of pore-size of the filter on the stability of the reconstituted product should be investigated.

1.3 The effect of agitation on the stability of the reconstituted and diluted products should be investigated.

1.4 Aglucerase is unstable and prone to oxidation; the Company should comment on the rationale of the manufacturing process in order to avoid potential degradation during manufacture.

PART IIB

2. The manufacturing formula should be clearly presented in the tabulated form containing the exact amount of aglucerase and excipients at scale-up.

3. Confirmation should be given that a potency check of the bulk drug will be included prior to the manufacture of the finished product.

4. Sterilisation

4.1 The prefiltration bioburden should be reduced.

4.2 The holding time of the filtered bulk solution prior to lyophilisation should be provided.

C3 cont.

Number:

CPMP 12375/0001-2

Company:

GENZYME BV

Product:

CEREDASE 50 IU AND 400 IU

Therapeutic Class:

ENZYME

Active Constituent:

AGLUCERASE

4.3 Further information on the validation of the lyophilisation step including the issue of microbial control should be provided.

5. Details of the manufacture of human serum albumin including its sterilisation should be provided.

6. It is noted that the formulation of the bulk solution is carried out in Massachusetts and sterilisation is carried out in New Mexico. The Company should provide details of the transport of the bulk solution including transit time and microbial control. The issue of stability during transport should be adequately addressed.

PART IIC

7. Further details should be provided on the handling, storage and control of the human placentae, including information on the screening and testing of placental donation.

8. An appropriate specification for the ethanol extract manufactured by Imedex in France should be provided, including the control of viral contamination.

9. Manufacture of Phenyl column eluate

9.1 It is noted that the phenyl column eluate can be stored for up to 6 months. The data seemed to suggest that up to 10% of loss of potency could occur. The company should comment on the significance of this finding in relation to the proposed holding time.

9.2 The stability of the eluate during freezing and thawing should be investigated.

9.3 Details of the thawing procedure including environmental conditions and thawing time should be provided. The proposed thawing procedure should be justified on the basis of validation data.

10. The holding time of the carboxymethyl (CM) sepharose column eluate should be justified with experimental data. The storage conditions should be detailed.

Number:

CPMP 12375/0001-2

Company:

GENZYME BV

Product:

CEREDASE 50 IU AND 400 IU

Therapeutic Class:

ENZYME

Active Constituent:

AGLUCERASE

11. Specification for the Phenyl Column Eluate

The specification should be revised and limits for GlcNAc, Galactose and mannose should be tightened in line with the submitted validation data. A specification for total protein should be included.

12. Purification

12.1 Pertinent chromatographic details including chromatograms in relation to the fractionation process should be provided.

12.2 In the absence of any full-scale production batch analysis results, further experimental data should be provided to justify the loading capacity at scale-up.

12.3 The rationale and adequacy of the purification steps after enzymatic modification step should be commented upon, and adequate validation data should be provided.

12.4 An assurance should be given that preparations 3 to 6 will not be used to manufacture aglucerase.

* 12.5 Further consideration and validation on the viral inactivation should be provided.

12.6 It is noted that a recovery of >105%, and in some cases >115%, can be achieved after the phenyl column stage. The company should comment on the submitted data.

12.7 The company should comment on the variability of recovery data particularly for the carboxymethyl (CM) sepharose column where the percentage recovery increased from 73% (cycle 9) to 98% (cycle 20).

12.8 The storage, conditioning, and re-use time of the columns should be clearly stated.

13. An assurance should be given that reprocessing of the drug substance will not occur.

14. Characterisation of Aglucerase

Experimental data on the characterisation of aglucerase should be provided including the submission of key chromatograms and/or spectra.

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15. Analytical Methods

15.1 For the SDS-PAGE and GPC analyses, molecular weight markers should be clearly labelled.

15.2 Limit of detection or limit of quantitation should be clearly stated for the method used for purity check.

15.3 If the SDS-PAGE is the chosen method for purity check, the gel should be loaded appropriately to improve the detectability of the impurities present at low concentrations.

16. Drug Substance Specification

16.1 The proposed specification should be revised. The proposed limits should be tightened in line with batch analysis data.

16.2 The proposed purity limit using SDS-PAGE ≥85% is inadequate. Appropriate limits for impurities should be included using a validated method.

16.3 It is noted that potency is expressed in international unitage. It should be clarified which international standard would be used to determine potency.

16.4 It should be confirmed that the 4-methylumbelliferyl-ß-glucopyranoside (4-MU-Glc) would not be used in the future and that the potency of a sample is determined against a suitable reference standard for each batch of analyses (applied also to the finished product specification). Standardisation of the chosen method should be detailed.

16.5 Monosaccharide analysis and appropriate limits should be included or its absence justified.

17. Batch analysis

17.1 First five consecutive full-scale production batch analysis results should be provided.

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17.2 Pre-clinical batch analysis data should be provided.

17.3 Qualitative and/or quantitative analytical data of the batches manufactured by the other manufacturing and purification methods should be compared with that of the proposed method.

17.4 Additional bands were found in the SDS-PAGE results. These bands should be identified and clarified particularly in relation to the consistency of the product on a batch to batch basis.

18. Confirmation should be provided that physical tests such as fragmentation would be performed on the rubber closures in accordance with that in Ph.Eur. monograph.

19. Since aglucerase is unstable, it is unclear how frequently a new working standard is established. Calibration of the working standard against an appropriate standard should be clarified.

PART IIE

20. Finished Product Specification

20.1 The appropriateness of using the SDS-PAGE to check the purity of the product should be commented upon including the maximisation of the resolution of human serum albumin and aglucerase; otherwise, an alternative method should be developed.

20.2 The proposed limits should reflect the values seen in the batch analyses.

20.3 The Ph.Eur abnormal toxicity test should be included or its absence justified.

21. Batch analysis

Analytical results of the first three full-scale production batches manufactured at the proposed sites should be provided.

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PART IIF

22. Stability

22.1 Further stability data should be provided particularly for the 400 IU formulation.

22.2 The method used to determine the stability/purity of this product should be selective and discriminatory.

22.3 Quantitative and/or qualitative account of the stability of Ceredase including the reconstituted product in the presence of light should be studied.

22.4 Further experimental data should be provided to demonstrate that Ceredase is compatible with the 0.9% sodium chloride, 5% Dextrose Injection and the giving-sets commonly used in the European Community.

PART V

23. Ceredase should be subjected to product monitoring.

24. Confirmation should be given that full quality control in accordance with the Finished Product Specification will be carried out by a suitable establishment within the European Community.

25. A BAN should be applied for.

26. Labelling and Summary of Product Characteristics

Labelling and the SPC should be amended:

26.1 Subject to the resolution of point 22.3, the product and reconstituted product should be protected from light.

26.2 In line with good microbiological practice and subject to the resolution of points 22.3 and 22.4, the reconstituted product should be used immediately or otherwise justified.

26.3 Subject to the resolution of point 1.2, appropriate instructions should be included in relation to the use of an in-line filter.

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26.4 Subject to the resolution of point 1.3, clear instructions should be included on the reconstitution procedure with particular reference to shaking.

26.5 That the statement "do not freeze the product" should be included.

26.6 Subject to the resolution of 22.4, it should be emphasised that only the recommended diluents should be used.

26.7 It should be emphasised that Ceredase should not be mixed with other drugs.