DEPARTMENT OF HEALTH AND SOCIAL SECURITY
MARKET TOWERS
1 NINE ELMS LANE
LONDON SW8 5NQ
Telex 883669
Telephone 01-720 2188 Ext

Your reference
Our reference

Mr R. B. Christie,
Clinical & Technical Affairs Director,
ARMOUR PHARMACEUTICAL COMPANY LTD.,
St. Leonard's House,
St. Leonard's Road,
EASTBOURNE,
East Sussex BN21 3YG.

8th July, 1988.

Dear Mr Christie,

APPLICATION THROUGH THE COMMUNITY CONCERTATION PROCEDURE.
MONOCLATE LYOPHILISED POWDER.

Acting as the United Kingdom rapporteur for the Committee for Proprietary Medicinal Products, I am writing to convey to you points raised by some of the EC Member States, and on the issues of quality discussed and agreed at the CPMP Working Group on Biotechnology/Pharmacy held on June 7/8 1988.

The points can be divided into those affecting safety, efficacy and quality. You are formally requested to provide additional information on the points, and the time limits for consideration of the application (as set out in Article 4 of Directive 87/22/EEC) are therefore suspended. The Committee for Proprietary Medicinal Products is being notified of this suspension of the time limits.

Safety.

1. There was insufficient evidence of safety. In view of the transmission of HIV by a previous Armour product with an identical heat treatment schedule, an efficacious virucidal procedure against HIV should be applied to the product. Dry heat at 60°C for 30 hours was adequate.

2. Points raised by the Danish authorities, but the answers to which should be conveyed to all other concerned Member States:

   2.1. There is insufficient long-term evidence on the antigenicity of antibodies against murine proteins.

   2.2. There is insufficient evidence regarding neo-antigens in this preparation.

   2.3. The treatment period and number of patients is too low to provide a final assessment of safety.

AR-626168

3. Efficacy (Danish point).

It is unknown whether the efficacy of Monoclate is

4. Quality (Points agreed by the CPMP Biotechnology/Pharmacy Working Group).

These are listed in Appendix I to this letter.

After consideration of the above points you are invited to review them with the professional secretariat of the UK authority here at Market Towers, to informally discuss both the nature and content of these points, and the possibilities of future action for Armour in regard to this application through the concertation procedure. If you would contact me first of all, I should be pleased to arrange for this discussion. You will no doubt wish to ensure that you bring to the discussion experts (presumably from the US) able to fully address the issues raised.

This letter is copied to the CPMP Secretariat and other EEC Member States concerned with your application through this procedure or involved in national applications.

Other EC Member States have not completed fully their consideration of the application and the UK assessment report and, if there are any other points, these will be communicated to you later.

Yours sincerely,

GRO-C

A C Cartwright,
Superintending Pharmacist,
Pharmaceutical Secretariat.

AR- 626169

ARMOUR001833

ARMO0000212_0002

APPENDIX I

A. OBJECTIONS RELATING TO QUALITY.

A. Annex IIB : Method of Preparation.

The method of preparation is considered unsatisfactory unless the following are adopted.

1.1 an effective heating cycle should be adopted. The heat inactivation cycles should be fully characterised, and its effect on the stability of the product reported.

1.2 a suitable viral inactivation study should be undertaken, taking note of factors affecting survival, using representative hardy viruses of appropriate groups. Hepatitis viruses in particular should be considered.

1.3 validation of the purification procedures is required. There was concern regarding the reproducibility of the column chromatography steps as a viral inactivation procedure for HIV.

1.4 limits for microbiological bioburden at various critical production stages should be given. Columns should be sterilised where possible by autoclaving. Other decontamination procedures should be justified and validated.

1.5 the lyophilisation cycle should be described and how container integrity is demon strated.

A2. Annex IIC : Control of starting materials and reagents.

The specifications for materials and the manufacture and control of the reagents including the monoclonal antibody were inadequate.

2.1 The countries from which blood is collected for production of both Factor VII and human serummm albumin should be stated and found acceptable. The HSA should comply fully with the Eur. Ph. monograph and be pasteurised in its container. The documentation used should allow individual donations used in specified batches to be traced. The procedure for ensuring that batches containing donations from late HIV converters are rejected, should be specified. Details of testing for other retroviruses should be specified.

AR-626170

ARMOUR001834

ARMO0000212_0003

2.2 Full appropriate specifications should be provided for all starting materials and columns used in production.

2.3 The procedure for purification of the monoclonal antibody should be validated particularly in regard to viral inactivation. The antigen used to make the monoclonal antibody and its specificity should be fully characterised. The specification for IgG content should be tightened or justified.

2.4 Materials covered by BP/EP monographs including the final product should be tested in conformity with the appropriate monographs.

2.5 Full details of the production and control of the columns are required including measures to ensure that any potential contaminants arising from their single and repeated use, do not compromise the quality and safety of the final product.

A3. Annex IIE : Control Tests on the Finished Product.

Potential impurities (in the finished product) should be discussed. Consecutive batch analyses, showing their impurity profiles should reported. Results should be used to justify the specification. The allowed reconstitution period should be reducted to reflect the batch data. The specification for excipients content should be tightened and the full formula clearly stated. The potency limits should be tightened or justified. Photographs should be supplied as appropriate for gels and Western blots etc. Non - Eur. Ph. tests should be validated against Eur. Ph. methods.

A4. Annex IIF : Stability tests.

Further data on stability testing of a suitable number of batches using appropriate tests and statistical analysis should be provided.

B. ADDITIONAL POINTS REQUIRING CLARIFICATION.

Annex IID : Control tests on intermediate products.

It is not clear why the application discusses production conditions for the monoclonal antibody and Factor VIII C in this section. The tests and their associated limits applied to partially purified Factor VIII C are what would be expected.

The Company should consider testing the product for the presence of HIV antigen.

Diluent. The diluent should be sterilized in its container to receive a minimum Fo = 15 (NB Separate CPMP application).

4. Quality (Points agreed by the CPMP Biotechnology/Pharmacy Working Group).

These are listed in Appendix I to this letter.

After consideration of the above points you are invited to review them with the professional secretariat of the UK authority here at Market Towers, to informally discuss both the nature and content of these points, and the possibilities of future action for Armour in regard to this application through the concertation procedure. If you would contact me first of all, I should be pleased to arrange for this discussion. You will no doubt wish to ensure that you bring to the discussion experts (presumably from the US) able to fully address the issues raised.

This letter is copied to the CPMP Secretariat and other EEC Member States concerned with your application through this procedure or involved in national applications.

Other EC Member States have not completed fully their consideration of the application and the UK assessment report and, if there are any other points, these will be communicated to you later.

Yours sincerely,

GRO-C

A C Cartwright,
Superintending Pharmacist,
Pharmaceutical Secretariat.

AR- 626173

ARMOUR001837

ARMO0000212_0006