DOCUMENT 8

PHARMACEUTICAL EXAMINER'S REPORT

1. BACKGROUND

1.1 This product has been available on a named-patient basis for nine years for the treatment of haemophilia in patients producing neutralising antibodies ('inhibitors') to Factor VIII.

1.2 Appendix 1 outlines the coagulation cascade (taken from Hoffbrand and Pefit "Essential Haematology", 2nd Ed., Blackwell 1984) and shows that the formation of activated Factor X, or Factor $X_a$ is dependent on Factors VIII, IXa, $Ca^{++}$ and Platelet Factor 3. The company believe that FEIBA shows some activated Factor X-like activity and hence 'bypasses' the Factor VIII inhibitors, although the precise mode of action is still unknown.

1.3 The application for a product licence for FEIBA was received in September 1981 and was found to be inadequate in a number of respects relating to quality. Information on the manufacturing process was lacking, together with data on the stability of reconstituted product, the house standard used to measure Factor Eight Inhibitor Bypassing Activity, and labelling and data sheets particulars. The company were informed of these points of deficiency in a letter of the 19th March 1982 and submitted a written representation in October of that year.

Following consideration of this written representation by CSM in July 1983 the points of quality still outstanding may be summarised as follows:

CSM point 3.4 Full details of the ethylene oxide sterilisation procedures for all components should be provided.

3.6 Further details were needed on the house standard used in potency control.

3.7 Satisfactory product particulars and labels should be supplied.

2. DATA SUBMITTED

In October 1984 the company submitted a dossier for consideration by Medicines Commission which sets out to answer the above points in relation to the product FEIBA. Furthermore in December 1984 they submitted an additional volume of data relating to heat treatment of this material which they propose to call FEIBA-TIM4 to differentiate between the two products.

3. ASSESSMENT

3.1 The assessment below treats the company response to the outstanding points of quality together with the additional data on heat treatment and Medicines Commission is asked to consider whether there is now sufficient satisfactory information on the manufacture and control of the product to enable a licence to be granted.

8.I

3.2 CSM point 3.4
(Dossier pages 1, 2, enclosures F and G)

The product is supplied with a range of administration devices, transfer needles and aeration needles manufactured by Transcodan and Monoject (Sherwood). Information from these companies is summarised in enclosures F and G, where the materials are defined and the sterilising conditions described in more detail; in particular, ethylene oxide residues are limited to less than 2 ppm. No information is given on ethylene chlorohydrin or glycol levels but these are unlikely to be significantly different from the oxide level.

Transcodan and Monoject are the suppliers of administration devices for several products currently licensed in the UK.

3.3 CSM point 3.6
(Dossier page 2 enclosures H and I)

The house standard is briefly described as a plasma from haemophiliacs showing a high antibody titre to Factor VIII and it is suggested that "Factor VIII Inhibitor Plasma for FEIBA Standardisation" would be a more appropriate term.

A previous concern has been the variability in this plasma leading to unsatisfactory control of the finished product; however, this dossier suggests that each new batch of inhibitor plasma will be calibrated against the existing 'house standard' and in tests using a production batch of FEIBA. In addition, enclos. I contains comments from Dr. D.P.Thomas of NIBSC who has examined the standard and anticipates no problems in consistent control of the product, especially as it will be tested in his laboratories under the batch release procedure prior to marketing.

3.4 CSM point 3.7
(Dossier page 2)

The company refer to a previously submitted letter containing draft details of labelling and data sheet.

These details appear again (in modified form) in the volume of data on heat treatment.

3.5 Additional data on heat treatment

3.5.1 It has long been accepted that biological medicinal products derived from body fluids may be liable to contamination with viral pathogens and heat treatment has come to be recognised as a potential means of reducing this risk if the stability of the product allows it.

For example, albumin solutions heated to ca. 60°C for 10 hours have a considerably reduced risk of transmission of hepatitis. More recently the possible transmission of AIDS in Factor VIII concentrates has prompted the DHSS to request that all licence holders for Factor VIII should vary their process to include a validated heat treatment stage, so that all material on the UK market is of the heat-treated form.

8.2

3.5.2 In this case, the product at the stage of "Bulk Powder I" is heated in the dry state to 80-81°C for 10 hours, validated in a study using one model virus.

An electrophoresis pattern indicates no changes in the molecular integrity of the product which would lead to novel antigenic properties. Experimental results showing in vitro potency changes are absent.

3.5.3 Labelling and data sheet particulars are provided, modified to state that FEIBA-TIM4 is a heat treated product; the data sheet contains a reference to the reduced risk of transmission of viral disease.

4. SUMMARY

The precise nature and mode of action of FEIBA remain unknown. The company have addressed all the outstanding points of quality raised by the CSM and in addition have supplied information on a heat treated product, FEIBA-TIM4, which is claimed to reduce the risk of virally-transmitted disease.

Medicines Commission is asked to consider whether there is now sufficient satisfactory information on the manufacture and control of FEIBA and heat treated FEIBA to enable a product licence to be granted.

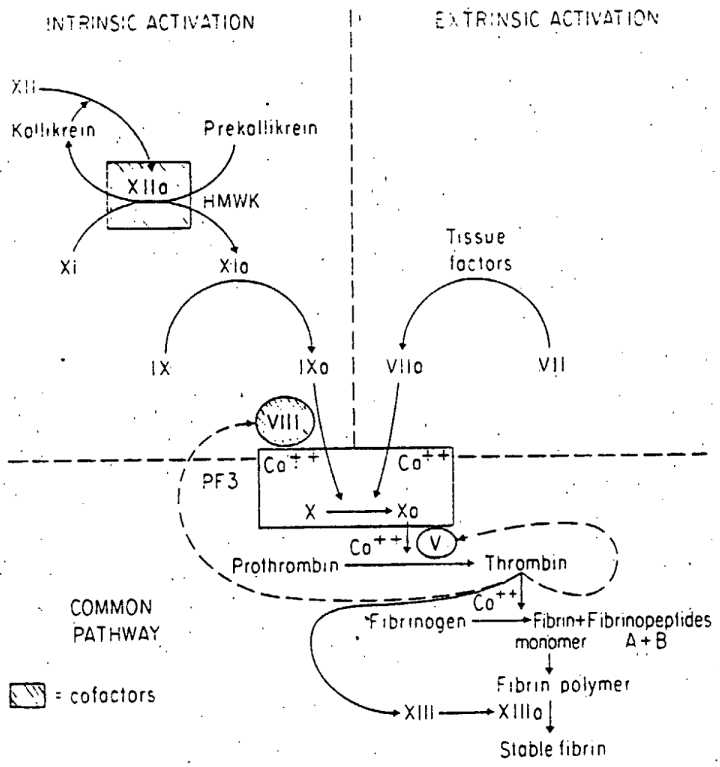
GRO-C

GRADE

10.6.85

8.3

Appendix 1




The pathways of blood coagulation.