Armour Pharmaceutical Company Limited

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WJT/SLS

22nd December 1983

D.H.S.S.
Market Towers,
1 Nine Elms Lane,
Vauxhall,
London SW8 5NQ

Attention of Mr. R. M. Saunders.

Dear Sirs,

CTX 0231/0070A Heat Treated Factorate
Extension - Pharmacokinetics

We wish to extend our studies on Heat-Treated Factorate, covered under the above CTX to include investigation of the Pharmacokinetics. The study will be carried out, in accordance with the enclosed protocol, by Dr. C. Rizza who is already included as an investigator in the particulars of our CTX.

We would be grateful for early confirmation that we may proceed with this investigation.

Many thanks,

Yours faithfully,
for ARMOUR PHARMACEUTICAL CO. LTD.

GRO-C

W. J. Tarbit
Assistant Regulatory Affairs Manager

enc:

I. INTRODUCTION

The management of haemophilia is complicated in many patients by the occurrence of liver disorders. Hepatitis A is not a problem and the modern methods of screening donors has helped to reduce the risk of hepatitis B infection. However, the non-A non-B hepatitis is a major problem. With the causative agent not yet identified its control has presented many difficulties. It now appears that it may be possible to eradicate the non-A non-B virus and a new FVIII preparation has been developed.

As only a limited number of patients will present each year in the U.K. who will be suitable for assessment of this new heat treated product it is most important that they should be entered into a controlled study with the information generated disseminated to U.K. Haemophilia Centres for meaningful evaluation.

It is proposed that the following pharmacokinetic study should be conducted as the first step in evaluation of Armour Heat Treated FVIII.

II. OBJECTIVES

To determine :-

1. FVIII potency in vitro
2. FVIII half life and recovery
3. Any change in protein species or product profile

in 4 - 6 patients with severe haemophilia A and treated with Armour Heat Treated FVIII.

III. INVESTIGATORS AND INSTITUTIONS

The study will be conducted by:

Dr. C. Rizza - Oxford Haemophilia Centre

IV. DESIGN AND SYNOPSIS

The study will enter a limited number (e.g. 4 - 6) of patients with severe haemophilia and be a straightforward pharmacokinetic study with the emphasis on the half life/recovery.

V. MATERIALS AND METHODS

1. Patient Selection

4 - 6 patients with severe haemophilia who have received numerous transfusions (more than 10 thousand units/annum and at least 1 infusion/month).
FVIIIC activity <1% of normal.
No evidence of inhibitors.
Aged 18 years and over.

2. Patient Exclusions

Patients with mild haemophilia.
Patients with inhibitors.
Patients with evidence of thrombocytopenia.

3. Procedures

a) Factor VIII
FVIII C
full recovery in vivo
t/2 in vivo
Rag
APTT

b) Haematology

Hb, RBC, WBC, differential absolute lymphocyte count.

c) Immunoglobulins

IgG, IgM, IgA, appropriate serology for viral infection.

d) Other Determinations

Urea, Electrolytes, Liver function tests.

e) Study Medication

Armour I.P. Heat Treated FVIII. A minimum of 2 batches is desirable for the study to ensure confidence in batch reproducibility.
A single dose will be administered to the patient. The infusion will contain 40 - 50 u/Kg and be administered over approximately 10 - 15 minutes.

f) Blood for Examination

will be withdrawn from the contra lateral arm in which a venous line may be placed.

VI. DATA RECORDING

The data will be entered on specially designed forms.

On Entry

1. History of the haemophilic condition (coagulation defect, severity, etc.)
2. Physical examination complete with special attention to lymphadenopathy and splenomegaly.
3. Laboratory procedures V. 3. a, b, c, d.

Follow-Up

FVIII profile and efficacy (VIIIC & APTT) will be determined at 5, 15, 30 and 60 minutes and 2, 5, 8, 12, 24, 36, 48 and 60 - 72 hours post-dose at the discretion of the physician.

Discharge

On completion of the study and prior to discharge, procedures b, c, and d will be repeated.

VII. ADVERSE REACTIONS

Any untoward event will be recorded by the investigator, the appropriate treatment administered, and a detailed report submitted.

VIII. ETHICAL APPROVAL

Ethical approval will be obtained from the centre conducting the study.

IX. WRITTEN INFORMED CONSENT

Written informed consent will be obtained.