BLOOD PRODUCTS LABORATORY

National Blood Transfusion Service

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28th February, 1985

Dr. Mary Duncan,
D.H.S.S.
Health Services Division,
Hannibal House,
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London,
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Dear Dr.Duncan,

Manufacture and Issue of Heat Treated
Coagulation Factor Concentrates by BPL

Further to our telephone conversations in December and January I am writing to outline the approach that BPL is adopting with regard to the manufacture and issue for clinical use of heated concentrates of factor VIII and factor IX. I apologise if my failure to write sooner has caused embarrassment.

Factor VIII Concentrate

The development at BPL of an improved concentrate, suitable for heat treatment (or other viral inactivation procedure) effective against hepatitis viruses, was already well under way when the AIDS storm broke in the summer of 1984 so that BPL's response here is in two parts :

i. issue of a heated variant of the existing intermediate purity product (coded HL(H)), as BPL's best instant response to the demand for 'something heated':

ii. controlled clinical trial of an improved heated higher purity concentrate (coded 8Y) followed by general release after submission of an abridged licence application based on data acquired from the trial.

We are working to the following 'timetable' :

Stage 1 - 100 vials of the HL(H) concentrate were issued to each of the haemophilia reference centres earlier this month for a preliminary evaluation of safety and efficacy in named patients. The first reports on these infusions are being received and indications are that the product was well tolerated and shows the expected in vivo recovery and half-disappearance time.

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Dr.M.Duncan 28th February, 1985

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Stage 2 - General issue of the HL(H) concentrate will begin as soon as information from the preliminary evaluation has been assessed (probably first week in March). Issue will be to designated clinicians for the treatment of previously named patients, but dispatch will be via Regional Transfusion Centres in order that resources can be seen to be satisfactorily allocated between Regions. A comprehensive protocol for follow-up of treatment was circulated in advance to all haemophilia centre directors (I enclose a copy - App.I) but I do not anticipate a very complete response. We will however be making the strongest possible recommendation that the first dose of the concentrate to any patient be given under medical supervision.

Stage 3 - During the last week in February limited supplies (~200 vials in all) of the heated high purity concentrate, 8Y, will be issued to selected haemophilia centres for a trial of immediate safety and efficacy in named adult patients. By mid-March we expect to have observations on subjective and measured response to the infusions, absence of reactions and half-disappearance time of factor VIII.

Stage 4 - Towards the end of March, the summarized results on data from stage 3 will be made available to other selected haemophilia centres, and directors of these centres will then be invited to request a supply of the 8Y concentrate for the treatment of named patients meeting the following criteria :

(a) not suspected of having liver disease at presentation;

(b) not having received more than two infusions of blood products in the last 12 months;

(c) not having received any blood products in the last 6 months;

(d) serum negative for HBsAg, anti-HBs and anti-HBc;

(e) giving informed comment.

I enclose a copy of the protocol for this study also (App.II).

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15 - 222

Dr.M.Duncan 28th February, 1985

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Stage 5 - Armed with the safety and efficacy data from stages 3 and 4 we would propose to make an abridged licence application for the 8Y product (hopefully early in May). After licence for the 8Y product has been granted, and when stocks of the concentrate permit, general distribution of 8Y will begin, the HL(H) product being phased out.

We look forward to stage 5 being complete by the end of June. You will notice that both protocols for patient follow-up place at least as much emphasis on hepatitis as on AIDS (HTLV-III). This reflects our conviction that NANB and type B hepatitis viruses present a more severe challenge to viral inactivation procedures than does HTLV-III.

Factor IX Concentrate

Our approach here has been more conservative than that of fractionators in North America. Recognizing that prothrombin complex concentrates are potentially thrombogenic, we were concerned that the freedom of heated factor IX concentrates from potentially thrombogenicity should be adequately demonstrated before any clinical trial. Although a small number of Christmas disease patients, whose only recorded treatment is with NHS factor IX concentrate, are now known to be HTLV-III antibody positive, we believe our original assessment of comparative risks was probably reasonable. We therefore intend to submit the heated factor IX concentrate presently being developed to extended testing in a dog model prior to clinical trial.

We would see clinical trial of the heated factor IX concentrate following the pattern of stages 3 to 5 above, but lagging two to three months behind the 8Y concentrate at all stages. As with 8Y, we intend to make an abridged licence application for the new heated factor IX concentrate before commencing general issue.

I would be most grateful for your comments on the procedure I have outlined. I would also be glad of an opportunity to discuss with you the precise form that licence applications for these products might take.

Yours sincerely,

T.J.SNAPE
Head of Quality Control
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