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Dr. I. Franklin,
Queen Elizabeth Hospital,
Edgbaston
BIRMINGHAM,
B15 2TH.

22nd October, 1986.

Dear Dr. Franklin,

I understand that tenders are soon to be sought for the annual West Midlands Regional contract for Factor VIII, following Armour Pharmaceuticals' recent withdrawal from the market.

As I would like the opportunity to give you all the information available about the safety and effectiveness of Koate HT, I have arranged an appointment with your secretary to see you on 23rd October. I thought, however, that you might find it useful to have the following information on Koate HT before we meet.

Source of Plasma

Koate HT is prepared from pooled human plasma from at least 1000 healthy donors. All donors are required to read and sign a confidential questionnaire which states that they are not members of any of the high risk groups for AIDS. In addition, a medical examination is routinely given to all donors to ensure good general health; this includes questions specifically related to AIDS-like symptoms.

No plasma is collected from the metropolitan areas of New York, San Francisco, Los Angeles or Miami where the majority of AIDS cases to date have been reported.

Screening of Plasma

Prior to pooling, each individual unit of plasma is tested and found non-reactive for hepatitis B surface antigen and antibodies to HTLVIII. Cutter Laboratories is also screening individual donations for alanine transaminase (ALT) levels. Any donation with ALT levels greater than twice the normal level is not used for production of Koate HT. By the end of this year, all batches of Koate HT will have been prepared from plasma screened for ALT levels in addition to HTLVIII antibodies and hepatitis B surface antigen.

Heat-Treatment

Koate HT is heated in the lyophilised form at 68^{o}C for 72-77 hours. The moisture content of the lyophilised

Heat-Treatment (Cont.)

concentrate is not more than 2.0%. This limit is set to ensure satisfactory stability of the product. The lyophilised powder is stable for 2 years at 2 - 8°C but can be stored for up to 6 months at room temperature (25°C) when required, such as in home treatment situations.

Virus Inactivation Studies: HIV

It has been demonstrated that an HTLVIII inoculum of 10^6 infectious particles/ml in the pre-lyophilised factor VIII concentrate is eliminated by the process used for production of Koate HT. Following lyophilisation and heat-treatment sy 68°C for 72 hours, no virus was detectable in the final product (Ref. McDougal et al, 1986 and J. Levy et al, 1985). Please see the inactivation booklet for a summary of results.

A clinical study conducted by a haemophilia study group in France, under the direction of Professor J.D. Allain provides further evidence that Koate HT carries no risk of transmission of HTLV (LAV). 11 patients with haemophilia A, 6 of whom had not been previously exposed to blood products were entered into this study and followed-up for up to 12 months following the initial infusion of Koate HT. No other blood product was given during the study. After at least 6 months, none of the patients studied for that period had developed antibodies to HTLVIII (LAV). (Abstract of paper presented at XVII International Congress of the World Federation of Haemophilia, Milan, June 1986).

The full report is not yet available but the data presented in Milan indicate that the heat-treatment process used in the production of Koate HT is effective in eliminating HTLVIII and also results in a significant reduction in the incidence of Non-A, Non-B hepatitis in haemophilic recipients.

The initial Non-A, Non-B viral inactivation studies carried out on Koate HT included a study in chimpanzees to demonstrate the effect of the heat-treatment process on the infectivity of non-A, non-B hepatitis. There was no evidence of hepatitis over a period of 15 weeks in animals inoculated with Koate HT which had been spiked with 2500 CID (chimpanzee infective dose) of NANB hepatitis virus prior to lyophilisation.

Further evidence of absence of non-A, non-B hepatitis and HTLVIII infectivity is obtained from clinical use of the product. Since it was first marketed in the USA in February 1984 and in the UK since February 1985, no reports of hepatitis non-A, non-B or HTLVIII antibody seroconversion in patients treated with Koate HT have been received from these or other markets worldwide.

Product Integrity after Heat-Treatment

The heat-treatment process used in the preparation of Koate HT not only preserves the product integrity, but also enhances its clarity and purity. The heat-treatment process that Cutter uses is the most rigorous of all commercial manufacturers'

Product Integrity after Heat-Treatment (cont.)

processes.

Koate HT has a biologic half-life of up to 13 hours (mean of 10.2 hours) and in vivo recovery has been shown to have a mean of 98.2%. The fibrinogen level is very low and reconstitution of the product is achieved in less than 2 minutes.

If you have any further queries, please do not hesitate to contact me.

Yours sincerely,

Anne Walton
Senior Sales Representative