1st Draft

Background

As early as 1968 Cutter Biological introduced Konyne, a preparation of factor IX complex, on to the market in the U.S.A. and in many other countries around the world.

An application for a U.K. product licence for Konyne was submitted by Cutter in 1982 but as the format was not in compliance with the DHSS guidelines, the application was unacceptable and subsequently withdrawn. For commercial reasons a re-submission of the data in the correct format was not pursued.

In 1984, following intensive work on methods designed to reduce the risk of transmission of potential infectious viruses in their coagulation products, Cutter completed the development of a heat-treated preparation of Konyne, Konyne-HT.

As the clinical use of Konyne was by then well established worldwide and the heat-treated product had been shown to be equivalent in terms of in-vivo biological activity and half-life to the non-heated product, no additional clinical trials were conducted with Konyne-HT.

The heat-treatment process employed in production of Konyne-HT is the same as that used for Cutter's dried factor VIII preparation, Koate-HT, for which a product licence was granted in February 1985 (PL0055/0107). This process had been demonstrated, prior to the grant of our product licence, to be effective in inactivating a number of model viruses including HTLV III/LAV.

It should be noted that the initial viral inactivation studies performed by Cutter in 1984 included some work on Konyne-HT as well as Koate-HT and no seroconversion to antibodies to HTLV III/LAV and no clinical signs or symptoms of non-A, non-B hepatitis have been reported in any patient receiving either product.

On the 8th May, 1985, Miles Laboratories submitted an application for a product licence for heat-treated Factor IX Complex, KONYNE-HT (PL 0055/0108) manufactured by Cutter Biological, Division of Miles Laboratories Inc., U.S.A.

In October 1985, the company received a Section 21 letter from the Committee on Safety of Medicines informing them that, on grounds relating to safety, quality and efficacy, they might be unable to recommend the grant of a Product Licence.

The Committee provisionally concluded that:-

1. Inadequate evidence had been provided on the manufacture and control of the sterile water for injection vials.

2. Inadequate information had been provided on the fractionation and control procedures.

3. Information should be provided on the standards used in finished product testing.

4. Inadequate evidence had been provided of virus inactivation.

5. Insufficient evidence had been provided of the clinical safety and efficacy of the product or of the product on which it is based.

This representation is Miles' response to the points raised by the Committee and includes additional information relevant to the grounds referred to above.

The Committee is asked to consider these documents in the knowledge that Miles Laboratories has requested a hearing.

Introduction

Factor IX Complex concentrates have been in use for about 25 years in the treatment of bleeding disorders associated with congenital deficiency of Factor IX in children and adults. They are also used for reversal of coumarin anticoagulant induced haemorrhage in emergency situations where prompt reversal is required.

It is well known that treatment of haemophiliacs with coagulation products fractionated from pooled human plasma carries the risk of transmission of viral agents. Of particular concern has been the risk of post-infusion hepatitis and more recently the development of Acquired Immunodeficiency Syndrome (AIDS).

In order to reduce the risk of transmission of infectious viruses, several steps have been introduced by Cutter over the past few years and included in their procedures for the collection and processing of the plasma used in the manufacture of coagulation products.

The following steps have been adopted by Cutter:-

1. The selection of healthy donors. Each donor is given a full medical and physical examination including history.

2. Screening of donors for antibodies to HTLV III and Hepatitis B surface antigen (? ALT ?).

3. The use of a heat-treatment process known to inactivate a range of viruses including HTLV III/LAV.

4. Testing of the final product for antibodies to Hepatitis B surface antigen.

In addition, strict adherence to Good Manufacturing Practice is employed by Cutter to eliminate the risk of contamination.

Further details of these procedures used in the production of Konyne-HT are included in Attachment 6 of this representation.

Further information on viral inactivation is presented in our response to point 4 of the Committee's letter in Attachment 4.

The evidence relating to clinical safety and efficacy is discussed in Attachment 5.

Our responses to the other points raised by the Committee are presented in Attachments 1, 2 and 3.

Attachment 1

1. Inadequate information had been provided on the manufacture and control of the sterile water for injection vials

Manufacture and Sterilisation

The water used for the formulation of Sterile Water for Injection U.S.P. is prepared by distillation from potable water which has been subjected to a series of treatments including deionisation prior to distillation.

The water is aseptically filled by membrane filtration through 0.22µ filters followed by terminal sterilisation in an autoclave which has been validated to assure final product sterility.

Each finished product sterilisation cycle is monitored with heat penetration temperature recording probes placed at the cold point of the autoclave chamber along with biological indicator organisms. The F_o value of the sterilisation process is at least 8.

Preparation of Containers

The containers (type I clear glass vials) are washed with Water for Injection and baked in dry heat ovens at 260°C for 4½ hours.

The rubber closures are washed and sterilised in an autoclave at 121°C for 30 minutes prior to use.

Both component processes are validated to assure end point sterility.

Specification

Sterile Water for Injection is tested for compliance with the requirements of the U.S.P.

The product, if tested, would comply with the requirements of the British Pharmacopoeia for Water for Injection.

Attachment 2

2. Inadequate information had been provided on the fractionation and control procedures

a) The reagents used to adjust the pH at the various fractionation steps are given on the flow sheet diagram presented on the attached pages

b) Details of the time cycles and temperatures used for sterilisation of equipment and final container are provided as follows:

Equipment

Bulk tanks are sterilised for 60 minutes at 122°C.

Filters are sterilised for 45 minutes at 121°C.

Final containers

Bottles are sterilised in the Tunnel Steriliser using infra-red heat at an indicated oven temperature of not less than 300°C for not less than 15 minutes.

Stoppers are steam sterilised under pressure at an F_o of not less than 22.4 at a temperature of not less than 120°C.

Equipment is steam sterilised under pressure at an F_o of not less than 22.4 at a temperature of not less than 120°C.

c) The specifications for sodium acetate, acetic acid and water use in the production process are as follows:-

- Sodium acetate U.S.P. + pyrogen tested. (Specification sheet attached, pages

- Acetic acid glacial U.S.P. + pyrogen tested. (Specification sheet attached, pages

- Water for Injection U.S.P. - prepared by distillation.

d) Sodium phosphate is used in the buffer used in the regeneration of DEAE-Sephadex.

e) Filters are integrity-tested before and after sterilisation using a bubble point and/or forward flow test.

f) The needles supplied in the product pack are sterilised with ethylene oxide.

Each batch is tested for sterility (U.S.P. test), pyrogens (LAL test) and Safety (tissue culture). Biological indicators are used at half and full cycles during the sterilisation process. Ethylene oxide residuals, safety, sterility and pyrogens are tested at full cycle.

Attachment 3

3. Information should be provided on the standards used in finished product testing

Since there are no international standards for NAPTT and Factors II, VII and X, Cutter use in-house standards and their use is approved by the FDA.

A number of 5ml vials from a batch of Konyne (freeze-dried) were set aside and suitably stored for use as the reference standard for NAPTT.

A special 5ml vial of Konyne-HT is used as the standard for potency assays.

The Factor IX unitage of the in-house standard was determined by assay against the WHO Factor IX standard.

Factors II, VII and X were assigned values by assay against three separate plasma pools from more than 10 donors. The standards are stored at -20°C or less.

The in-house standards will be calibrated against the WHO 2nd International Standard as soon as it becomes available.

Attach 4?

Attachment 5

5. Insufficient evidence had been provided of the clinical safety and efficacy of the product or of the product on which it is based

The clinical studies reported in our product licence application for Konyne-HT were conducted about 20 years ago on the non-heated product Konyne. Obviously these studies do not meet current standards for conduct of clinical trials but since, at that time, no further work was required in order to obtain registration of the product in countries where marketing authorisation was required, no further studies were undertaken.

However, as stated in our application, the use of factor IX complex in patients with haemophilia B is well established (see Martindale, 28th Edition, p. 328) and Konyne has been in use for this indication in a number of markets since 1968. Thus, in developing a heat-treated preparation of Konyne, it was deemed necessary to demonstrate only that the in-vivo recovery and biological half-life were the same in both products and it follows that efficacy in terms of raising the plasma level of factor IX activity in patients with haemophilia B would also be the same.

Furthermore, the properties of the product, as demonstrated in the in-vivo studies reported in our product licence application, were shown to be unaffected by heat-treatment. Thus, no difference in known side-effects were anticipated and the half-life study demonstrated similar patient tolerance and effects on haematological and biochemical parameters in the heated product to the observed effect in non-heated Konyne.

The important difference between the two products is the heat-treatment step, introduced in order to reduce the risk of transmission of infectious agents such as hepatitis B virus and HTLV III/LAV. As reported in Attachment 4 of this representation, no virus was detectable in the final heated preparation after pre-lyophilisation inoculation with a viral titre of ID-50 > 10 HTLV III/LAV.

The transmission of viral hepatitis has always been of concern in clinical use of antihaemophilic factor VIII or IX, and the evidence to date suggests that the heating process employed in production of Konyne-HT reduces this risk.

As reported in our product licence application, a study in chimpanzees demonstrated that the heating process inactivated a known amount, 2,500 infectious doses, of the Hutchinson strain of non-A, non-B hepatitis virus as well as an unknown quantity of endogenous non-A, non-B hepatitis.

The results showed that the hepatitis observed in control animals in this study was not due to hepatitis A or B virus or cytomegalovirus, but due to the infectious dose of non-A, non-B hepatitis virus with which they were inoculated either with spiked non-heated Konyne or as a separate inoculum.

No evidence of non-A, non-B hepatitis or hepatitis B infection was observed in animals administered heated Konyne with or without an inoculum of non-A, non-B hepatitis virus.

Clinical studies designed to investigate the possibility of transmission of non-A, non-B hepatitis have to be performed in patients who have not previously received blood products, that is, virgin haemophiliacs with haemophilia B. Quite apart from the ethics of conducting trials in these patients, the number of available patients is very small.

Cutter is currently monitoring the use of Konyne-HT in such patients but, so far, only two patients have become available for inclusion in the study and the study is not yet complete.

Although, as yet, we have no absolute evidence that heat-treated Konyne does not transmit non-A, non-B hepatitis in haemophiliacs, we have had no reports of non-A, non-B hepatitis in haemophiliacs receiving our dry heat-treated factor VIII preparation (Koate-HT) which has been in clinical use for several years. As the same heating process is used for both products and since factor VIII usage is much higher than factor IX, it would be expected that the possibility of a patients developing non-A, non-B hepatitis through administration of Konyne-HT would be very unlikely.

In conclusion, although all possible steps have been and are being taken by Cutter to reduce the risk of transmission of infectious viruses, the technology presently available does not allow us to claim with certainty that the product is completely free of infectious virus. The risk to the patient must be considered carefully in each individual case and balanced against the risk of depriving the patient of treatment with the product.

Attachment 6

(Details of screening procedures and product testing will be included here).