MEDICAL ASSESSMENT

INTRODUCTION

All anti-haemophilic factor (AHF) preparations can cause hepatitis, and most haemophiliacs will sooner or later get hepatitis. Some will die of it. Clearly anything that improves this situation would be desirable but it is important to distinguish which form of hepatitis poses the greatest threat. It is not hepatitis A because for all practical purposes this is not blood borne. Hepatitis B is transmitted by blood and blood products but since all blood and plasma donations are now routinely screened for hepatitis B surface antigen (HB_sAg), the possibility of transmission of hepatitis B virus (HBV) by blood or blood products has been considerably reduced. Non-A, non-B hepatitis (NANBH), on the other hand, cannot be tested but is thought to account for 90% of all hepatitis due to blood and blood products and to be more likely than HB to cause chronic liver disease. Notable exceptions to this rule are the preparations of albumin for i.v. use. These are pasteurised and the viruses which are certainly present in the untreated product are inactivated. This process is made possible by the use of stabilisers which protect the albumin from degradation (boiled egg!) during heat treatment. A similar process which could be applied to AHF has been sought for many years. Originally the product was too unstable for such treatment because of the impurities present. As quality has improved, so it has become possible to heat treat the product without too great a loss of yield. This is what all the manufacturers are now trying to do. The goal would appear to be a process which inactivates the hepatitis viruses without too great a loss of expensive coagulant activity and, not least, a product free of potentially dangerous degradation products. It would also be desirable if all viruses were inactivated, including for instance EBV and CMV. There would also be a wonderful reassurance to the haemophiliac population if it could be shown that the treatment protected them against the acquired immune deficiency syndrome (AIDS) but as the cause of AIDS is not known, any claims of this nature appear irresponsible at present.

PRODUCT PARTICULARS AND DRAFT DATA SHEET (See APPENDICES A and B).

These are broadly acceptable except for the final paragraph of the Draft Data Sheet which slips in the company's true intentions regarding the promotion of this product. The evidence submitted does not exclude transmission of hepatitis B although it is probably reduced. Transmission of non-A non-B hepatitis has been observed in at least one patient and possibly one chimpanzee.

CHEMISTRY AND PHARMACY

This will be dealt with in detail by the Pharmaceutical Assessor.

The plasma used for the preparation of FVIII HS appears to be satisfactory. Plasma is obtained from the US and is of Source Plasma (Human) quality only. The rest comes from German and Austrian blood banks under the control of the manufacturer, in which the German Red Cross recommendations apply.

There is not much real detail about the manufacturing process and in particular the heat treatment section. It can be deduced that sucrose and glycine are used as stabilisers but the justification for doing so, and for the concentrations used, is not stated in any detail, nor is anything said about residues of these substances and their impurities in the finished product.

It is almost impossible to discover the loss of yield attributable to heat treatment. The company have chosen to heat treat the product in solution rather

than the dry state. It is commonly believed that heating dry preserves yield but does not inactivate all the viruses, while heating wet inactivates very efficiently but destroys much of the yield. The application is unforthcoming on this.

The process does produce a product which on the face of it compares favourably with other AHF preparations. It has high potency, and is low in protein, fibronectin (CIG), plasminogen, fibrinogen and FVIIIR:Ag, which should improve its solubility and reactivity. Little is said, however, about possible degradation products. No detailed comparison has been made on a before and after heat treatment basis.

EXPERIMENTAL AND BIOLOGICAL STUDIES

Pharmacology

Three mongrel and eight beagle dogs were dosed i.v. with FVIII:HS at doses of 25, 50 and 100 u/kg and control given one after the other at intervals of 3-5 minutes. Cardiac and respiratory parameters were monitored during the injections and for 10 minutes afterwards. No significant changes were observed.

Toxicology

Rats and mice were given single i.v. injections of FVIII:HS at doses of 50-200 u/kg; rabbits received 100 u/kg, control animals received saline. Groups of 10 ♂ and 10 ♀ were used for control and each dose level in all three species. All animals were observed for 14 days.

There were no deaths. Nothing abnormal was noted except some loss of weight in rabbits from both control and treated groups.

Local i.v. tolerance was investigated using a tied-off vein in the rabbit ear. There was no reddening or thrombus formation.

Guinea pigs were used to test for new antigenicity and passive cutaneous anaphylaxis. Nothing abnormal was seen.

The product was spiked with CMV before heat treatment. After processing no cell-free virus was detectable. Cell-associated virus was still detectable but it is contended that, as the finished product is entirely cell-free, this poses no problem.

Special Testing for Freedom from Hepatitis Virus

Two studies were done using chimpanzees. In the first, two animals were given crude cyroprecipitate used as a starting material for AHF, which had been spiked with Hepatitis B Virus (HBV). Both developed hepatitis. The cryo was processed to finished product stage. Half was heat-treated, half was not. Four chimps were given the heat-treated product and another four were given the untreated material. Those who had the untreated AHF developed hepatitis B, the four who had the heat-treated product did not. One chimp in the heat-treated group had raised transaminase levels at 28 weeks and died of no apparent cause the following day. HBV markers were all negative and there was no jaundice. Liver biopsies were all normal. The company conclude that this was not HB. This is probably correct, but the possibility that it might have been Non-A Non-B Hepatitis (NANBH) cannot be ruled out although 28 weeks might be thought a

little too long for the incubation period usually associated with NANBH (2-26 weeks). The second study was similar. Two chimps were given the spiked starting material and three were given the heat-treated product. The first two developed HB, the others did not.

Clinical

Nine investigators in seven West German centres conducted seven open clinical trials in 78 patients, 74 of whom had haemophilia A, 2 were (female) haemophilia A carriers and 2 had von Willebrand's disease. Two of the investigators conducted a pharmacokinetic study while the other seven studied therapeutic and prophylactic use.

The disappearance of FVIII:C is usually reported as a simple half-life which measures the time from maximum concentrations to half that value. It is thus a composite of the rapid first phase and the slower terminal phase, and is of practical value in determining the amount of FVIII needed by individual patients. The reported values are usually in the range 5-10 hours. On the other hand, the biological half-life is usually about 12 hours. The study results are summarised as follows:

Investigator	N	Mean Initial Half-Disappearance Time (hrs) ± SD	Mean Half-Life (hrs) ± SD
Hellstern/08	5	4.3 ± 0.83	10.5 ± 6.44
Weisser/09	6	10.9 ± 5.09	13.4 ± 3.64
All Subjects	11	7.90 ± 4.99	12.1 ± 5.06

Results for the individual patients are attached as APPENDIX C.

In vivo recovery for AHFs is usually expressed as the percentage increase in circulating FVIII/unit/kg body wt or as percent recovery related to estimated plasma volume. Results from 66 observations on 50 subjects are shown in APPENDIX D.

The results are rather variable but they are not inconsistent with similar preparations which have not been heat-treated.

There was nothing unusual in the results of tests of coagulation.

Clinical evaluation for efficacy was carried out on 67 subjects, 57 of whom (85%) had a good or moderate clinical response. Efficacy appeared to be unrelated to the severity of the conditions treated. (APPENDIX E)

None of the 66 patients assessed for allergic, pyrogenic or local reactions and other side effects showed any adverse reaction.

Hepatitis B Serology

Thirty-four out of the 67 subjects were initially HB negative. Follow up serology showed no evidence of HB infection resulting from treatment with FVIII:HS. One patient became positive for HB_s and HB_c some 22 months after receiving FVIII:HS but having had untreated FVIII 5 months previously this seroconversion was not considered to be due to FVIII:HS.

Thirty-six patients were followed up clinically and one developed non-A non-B hepatitis (NANBH). The company claim that because the hepatitis occurred two years after the first administration it is unlikely to be product-related. In fact the patient had 78 administrations of FVIII:HS, a total of 130,380 units, most of which were given during a period in hospital for surgery, rather nearer to the onset of NANBH. The precise timing is not specified.

Those patients who were not followed up serologically were, for the most part, positive for HB markers pre-treatment.

On the basis of their series of 34 patients, the company made comparisons with US and Swedish studies which calculate risk factors for haemophiliacs developing HB as a result of receiving FVIII. The US study shows that only 10% of a group of 1,322 haemophiliacs were HB negative when seen and 40% of these had seroconverted six months later. Depending on how the FVIII:HS trial group are divided, the comparable figures are a maximum risk of 9% or 19% (N = 34 and 14 respectively). The comparison with the Swedish work suggests that the figures for FVIII:HS are an upper probability of 1 case of HB for every 250 administrations or 188,000 units compared with one case for 53,000 units when data from single donor cryo and commercial concentrate are pooled. The comparable figure for commercial concentrate alone is 1 : 6,800 units.

Seven patients had serum liver enzyme abnormalities during follow-up. Three of these were probably unrelated. Out of the remaining four, one almost certainly had product-related NANBH, while the other three had no clinical manifestation of liver disease.

The company's views on AIDS transmission are as follows:

Comment on Factor VIII Concentrates and the Possible Risk of AIDS

The acquired immunodeficiency syndrome (AIDS) is an acquired defect of cell-mediated immunity initially encountered predominantly in homosexuals and, more recently, in haemophilia A patients. The occurrence of AIDS in haemophiliacs is attributed to the fact that such patients depend on life-long treatment with Factor VIII concentrates obtained from large plasma pools. It is, therefore, not possible to rule out AIDS transmission because an infective agent stemming from AIDS-infected donors might potentially be present in the concentrates.

Behringwerke have developed a method for the production of hepatitis-safe products by heating plasma factors. This heating step inactivates not only the hepatitis viruses, but also for example, cytomegaloviruses. Since an infective agent or simultaneous infection with several viruses is under discussion as one of the possible causes of AIDS, these pasteurized products would provide additional safety.

MEDICAL COMMENT

1. On the evidence presented, this looks like a good AHF concentrate of satisfactory solubility, efficacy and safety. There is no evidence that it is any worse than comparable products which have not been heat treated, but the amount of data on which the comparison is made is not very extensive. Very little is said about possible physical and chemical changes produced by heat-treatment.

2. It is probable that hepatitis B will be less likely with FVIII:HS than with comparable untreated products, but the statement made in the Draft Data Sheet that it is "excluded" goes beyond the available data.

3. There is no evidence to suggest that heat-treatment will affect the transmission of non A non B hepatitis. The statement made in the Draft Data Sheet is wrong; at least one transmission is recorded in the application.

4. The comment on AIDS in the Chemistry/Pharmacy section represents irresponsible innuendo with regard to AIDS and includes the claim that the heat-treatment inactivates hepatitis viruses. Nothing in the application suggests that any hepatitis virus other than HBV is inactivated.

5. In spite of careful screening of all blood and plasma donations for HB_sAg, there is still a risk that AHF preparations will transmit hepatitis B to those who receive it. This product will reduce that risk but there can be no certainty at present that it will exclude it.

MEDICAL OPINION

That a product licence should be granted on condition that the Data Sheet makes no implied claims that cannot be supported by the evidence submitted.

1. Claims that transmission of hepatitis B is excluded rather than reduced should not be permitted.

2. Claims relating to the transmission of non A non B hepatitis should not be permitted.

3. No reference to AIDS should be permitted except as a warning that blood products may transmit the syndrome.