SUBMISSION FOR A PRODUCT LICENCE VARIATION FOR SNBTS FACTOR VIII ZB

EXPERT REPORT ON THE CLINICAL DOCUMENTATION

INTRODUCTION

I have been closely involved with the clinical evaluation of SNBTS Factor VIII products. This has included the carrying out of half-life and recovery studies on each of the SNBTS FVIII products manufactured to date.

i.e. FVIII NY unheated (PL 3473/0007)
FVIII NY heated at 68°C/2H (Unlicensed)
FVIII NY heated at 68°C/24H (Unlicensed)
FVIII ZB (The subject of this licence variation application).

Factor VIII ZB has been the concentrate treatment of first choice for my patients since its introduction into routine use in 1987. This is consistent with the view of the UK Haemophilia Reference Centre Directors report (Supplement 1) which recognises FVIII products which have been dry heat-treated at 80°C for 72 hours as being amongst the safest available products with regards to the risk of virus transmission.

A key component of this evaluation is the establishment of a study of infectivity in previously untransfused patients (PUP's). The protocol for this study is appended (Supplement 2) and is similar to the protocol used in the published study of the Factor VIII Product 8Y manufactured by the Blood Products Laboratory, Elistre.

I should comment on the clinical data supplied by the SNBTS as follows:

1. EFFICACY

The initial pharmacokinetic study carried out in my Department has been well described by Dr. Boulton. This study demonstrated that the product had a reasonable half-life with an acceptable recovery, although the levels of recovery were at the lower end of the range of data from similar studies using other Factor VIII products. It must be stated, however, that patient numbers were small and that patient variability may have contributed to the lowish levels of recovery observed in this study.

Haemophilia Directors in Scotland and Northern Ireland, in conjunction with the Factor VIII Working Party, are currently undertaking a study of the viral safety of Factor VIII ZB within the guidelines recommended by the International Society for Thrombosis and Haemostasis.

Shortly after the successful outcome of the pharmacokinetic study, the product was introduced into routine use. It has been used for routine treatment of 293 patients in Scotland and Northern Ireland with Haemophilia A. The product is efficacious in all patients treated, although some patients have reported that a higher dosage is required compared to treatment with the
previous product (Factor VII NY). It is not absolutely clear, however, whether this extra demand is due to a slightly reduced clinical effectiveness or due to increased usage caused by less fear of the virological sequelae of clinical use of this product.

I have concluded that Factor VIII Z8 is an effective haemostatic agent for the treatment of Haemophilia A.

2. SAFETY

The product has been well tolerated by all patients except one who had repeated allergic reactions to all infusions of Z8. These were less when the patient was treated with FVIII BY from the Blood Product Laboratory but still clinically unacceptable. The patient is currently treated with Monoclate (monoclonally purified factor VIII in albumen; Baxter). It is concluded that this is an idiosyncratic allergic reaction and that the product is well tolerated by the vast majority of patients.

There is no evidence of increased numbers of patients developing Factor VIII inhibitors following treatment with Factor VIII Z8.

The virus safety data available to date are highly encouraging. No cases of HIV seroconversion have been attributed to any batches of SBNTS dry-treated coagulation factor concentrate. A study of patients treated in my department revealed no seroconversions in patients treated with SNBTS NY heated at 68°C for 2 hours or 24 hours, even when the patients were later found to have been treated with product derived from HIV - antibody positive donations definitely. The available data on infectivity due to other viruses are fairly limited. However, no cases of virus transmission have been attributed to Z8 heated at 80°C for 72 hours. As mentioned earlier, a PUP study has been initiated recently. Complete data are available from 4 patients 3-5 months after receiving their first infusion (Ref: Volume 2, Section 5, page 44 and Appendix 2) and some data are available from a further 5 patients. This is a reassuring observation as most recipients of unheated Factor VIII products would have been expected to demonstrate enzyme abnormalities consistent with a diagnosis of NANB Hepatitis. All PUP's detected in Scotland and Northern Ireland will be enrolled in this study and their liver function monitored repeatedly. However, it is recognised that this will be a slow process as such patients are relatively uncommon. However, available data suggest that the current product may be of comparable safety to the BPL product BY which is also heated at 80°C for 72 hours.

In summary, Factor VIII Z8 has a good safety record and I shall continue to prescribe it.

3. ADVANTAGES AND DISADVANTAGES OF THE PRODUCT

Factor VIII Z8 is manufactured from volunteer blood donors following the recommendations of the Counsel of Europe's proposals that States should aim towards self sufficiency in the
provision of blood products. Being dry heated at a terminal step in the manufacture is an advantage compared to the incorporation of a virus inactivation step at an intermediate step incase of inadvertent contamination in the plant equipment. A further advantage of the heat treated process is that it potentially inactivates a wider range of viruses than the solvent/detergent technique which is only active against lipid coated viruses. Furthermore the product does not contain trace amounts of solvent/detergent or mouse proteins (as found in monoclonally purified concentrates).

The principal disadvantage of Factor VIII 28 concentrate is its low purity. This, along with its heat inactivation step, makes it a product which is slow to dissolve during reconstitution. The other disadvantage that has been readily apparent during my use of the product is the large variation between batches in the units of factor VIII per bottle. These criticisms of the product make it less acceptable to patients and hospital staff than some other available factor VIII concentrates. None, however, in my view are reasons for withholding the granting of a licence.

4. SUMMARY AND CONCLUSION

In summary, that Factor VIII 28 is a safe, effective treatment for Haemophilia A. In my view the clinical data presented in the Licence application is an accurate summary of the available data and it is my belief that this product should be fully licensed for routine clinical use.

Dr. C.A. Ludlam
Director of Haemophilia Centre and
Consultant Haematologist,
Chairman
Factor VIII Working Party for Scotland/Northern Ireland,
Department of Haematology,
Royal Infirmary,
Lauriston Place,
Edinburgh.
EH3 9YW
SECTION 5

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5.1 INTRODUCTION

This section of the licence variation application summarises the clinical information available on the use of the SNBTS Factor VIII Concentrate Z8.

Before Z8 product was released for routine use, its in vivo recovery and half-life characteristics were assessed in volunteer patients. This data is summarised in Section 5.2. in a report provided by Dr F E Boulton of the Edinburgh & South-East Scotland Blood Transfusion Service. The observed elimination half-lives of 9.3 - 18.1 (mean = 16.9 hours) falls within the expected range of 7 - 20 h (Allain, 1984). Mean recovery values of 89.3% are also within the expected range, although the observed values are at the lower end of the published range (Kasper, 1984). This data suggests that unstable or activated Factor VIII is not present in significant concentrations in this product.

Following the finding of acceptable in vivo recovery and half-life characteristics, Z8 was issued for routine therapy of Haemophilia A patients. Clinical observations on the use of the product are summarised in Sections 5.3 to 5.5, covering clinical effectiveness, adverse reaction reports and viral safety.
5.2 TRIALS OF NEWLY FORMULATED SNBTS FACTOR VIII CONCENTRATE "Z8"

5.2.1 Introduction

This report forms part of a submission for a variation of the Product Licence for therapeutic human factor VIII concentrate manufactured by the Protein Fractionation Centre of the Scottish National Blood Transfusion Service. The need for a variation has arisen because the manufacturers have modified the process of manufacture from large-pool donor human plasma in order to allow effective virucidal treatment.

5.2.2 Methods

5.2.2.1 Study Design

(a) Subjects

The subjects were four human adults with severe haemophilia A (baseline factor VIII levels <0.02 iu/ml).

They were clinically well at the time of the infusion, had no history of inhibitors to factor VIII, were not bleeding or pyrexial, were not taking medications and had not received any infusion of therapeutic factor VIII over the previous seven days. Immediately prior to infusion they were weighed in light clothing, and the weight recorded (Table 5.1).

(b) Dosage

2,000 units were taken from 10 vials - each labelled 200 units, and dissolved according to the manufacturers instructions in 20 mls of distilled water for injection. Complete dissolution was sometimes prolonged in a few vials (maximum 55 minutes). After complete dissolution, all but 1-3 mls (ie 197-199 mls) were infused intravenously over 17 to 25 minutes via a series of syringes (Table 5.1). No "premedication" (eg with corticosteroids or antihistamines) was given. The sample aliquots were made available for local assay (Table 5.1).
(c) **Clinical Observations**

The temperature, pulse and blood pressure were monitored and recorded from before infusion, throughout infusion and at intervals thereafter of 20 minutes, 60 minutes, 2 hours, 4 hours, 8 hours, 24 hours and 24.5 hours. Any signs of other adverse effects (rashes, bronchospasm etc) were to be recorded if they occurred.

(d) **Blood Sampling**

Venous blood was taken prior to infusion and at intervals of 20 minutes, 60 minutes, 2 hours, 4 hours, 6 hours, 24 hours and 24.5 hours after the end of the infusion.

5.2.2.2 **Assays and Other Tests**

(a) **Sample Processing**

Aliquots from each sample were taken at collection into citrate and the plasma separated and frozen rapidly for clotting studies to be conducted the following day. Samples were also taken into EDTA for full blood count.

(b) **Techniques**

Factor VIII assays were conducted by the one stage technique (Austen and Rhymes 1975) modified for use with the General Diagnostics "Coag-a-pet x 2" or the "Coag-a-mate". Dilutions of patient's plasma and of the standard were prepared in human plasma depleted completely of factor VIII by adsorption with immobilised murine monoclonal antibody to factor VIII (Diagen). The standard was the 13th British Plasma Standard. Assays were conducted in two separate laboratories (Edinburgh BTS and Edinburgh Haemophilia Centre); results are presented together.
5.2.3 Results

5.2.3.1 Clinical Responses

In three subjects no adverse responses were observed (Table 2). Pulse, blood pressure and temperature were stable throughout. Subject 4 experienced a slow rise in temperature from 36.4°C at 2 and 4 hours; this was settling by 6 hours. This man also experienced a subjective sensation of tightness in his chest after 5 minutes of infusion (50 mls) which was relieved immediately on slowing down the rate of infusion. No other objective signs of an adverse response were observed.

5.2.3.2 Factor VIII:C Responses

These are tabulated in Table 3 and plotted for each patient individual in Figures 5.1A and 5.1B. Table 5.4 details the calculated data of in vivo recovery and survival characteristics of the infused factor VIII.

5.2.4 Discussion

5.2.4.1 Clinical Observations

The results shown in Table 5.2 indicate that all subjects maintained a steady pulse and blood pressure. Subjects 1-3 revealed no change in temperature but subject 4 experienced a mild pyrexia which he did not notice. Neither did he regard the sensation of tightness in his chest as being significantly different from similar experiences during infusions of previous batches of factor VIII.
It would therefore appear justifiable to regard the significance of this reaction as dubious, particularly as the author was present and was impressed by the apparent relief which followed a reduction of the rate of infusion.

5.2.4.2 **Product Preparation**

It was noted by the nursing staff who reconstituted the product that the contents of a few vials took a long time to dissolve, even though scrupulous attention was given to adding the water at room temperature rather than at 4° C and to the avoidance of frothing during mixing. The vials were mixed very gently on a roller after the water was added. The process was similar, but not identical, to that of the manufacturers when the solubility of the product was assessed prior to approval for issue. No prolongations of reconstitution time to such a degree had, however, been noticed by the manufacturer. On close inspection of the clinical nursing staff practices, it is apparent that for many vials the bulk of the contents dissolved rapidly (within five minutes) but that a relatively insoluble residue sometimes remained, and the nursing staff always waited for this to dissolve completely. It is anticipated that this feature will improve in successive batches of Z8.

5.2.4.3 **Assay Results**

(a) **Comparison of Results from the Two Laboratories**

Table 5.3 reveals that some assays from the same samples, when conducted separately in the two laboratories, show wide differences. This is particularly marked for Subject 4 in whom there are two-fold discrepancies for some time-points.

Inter-laboratory variation of assays of VIII:C is well known. Both laboratories involved in this report participate regularly in quality assurance schemes run locally and nationally (UK NEQAS) with consistently satisfactory performances.
(b) In Vivo Recovery and Half-Life

Table 4 indicates that the half-disappearance times are well within the range expected from previous experience both in this centre and elsewhere. The recovery values are also within the range of previous studies but are at the lower end (see Nilsson et al 1973 for values of other manufacturers' products; results for previous heat treated SNBTS products given to subjects in this report are shown in Table 9.9). Inspection of the decay curves (Figures 5.1A and 5.1B) shows that Subjects 1 and 4 revealed a clearly defined separation into a first and second phase as is commonly found after infusions of therapeutic factor VIII. The decay of VIII activities in Subjects 2 and 3 are not biphasic. This is unexpected, but Hellstern et al (1986) reported a lack of two-phase decay response after infusion of steam-heated factor VIII. However, these responses also showed a prolonged survival.

5.2.5 Conclusion

Four subjects, who are severe haemophiliacs, have been infused with a new therapeutic concentrate of human factor VIII prepared by the Scottish National Blood Transfusion Service. The contents of occasional vials took longer to achieve complete solution than is usual.

No immediate or delayed adverse responses of clinical significance were observed although one subject experienced a subjective sensation of tightness in his chest early during the infusion: he also displayed a mild pyrexia (37.5°C) 2 to 4 hours after infusion which he did not notice. In the light of his similar subjective experiences with other therapeutic infusions of factor VIII before, this reaction is probably not of any significance.

Recovery of factor VIII in the plasma of each subject was satisfactory but at the lower end of the normal range. Half-disappearance time in plasma in vivo was well within the normal range.

This new formulation of therapeutic factor VIII concentrate is acceptable for the treatment of men with severe haemophilia.

F E Boulton
10 August 1988

(LICENCE APPLICATION : FVIII/28)
### TABLE 5.1

**SUBJECT AND INFUSION DETAILS**

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>SUBJECT 1</th>
<th>SUBJECT 2</th>
<th>SUBJECT 3</th>
<th>SUBJECT 4</th>
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<td>Age (yrs)</td>
<td>26</td>
<td>39</td>
<td>19</td>
<td>47</td>
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<td>Weight (kg)</td>
<td>53.0</td>
<td>54.4</td>
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<td>78.4</td>
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<td>Infusion volume (ml)</td>
<td>199</td>
<td>198</td>
<td>198</td>
<td>197</td>
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<td><strong>Product Potency VIII:C (IU/ml)</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>assigned by manufacturer</td>
<td>9.35</td>
<td>9.35</td>
<td>9.35</td>
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<tr>
<td>local assay</td>
<td>9.70</td>
<td>8.70</td>
<td>8.3</td>
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<td><strong>Dose (IU/kg)</strong></td>
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<tr>
<td>from manufacturing potency</td>
<td>35.1</td>
<td>34.0</td>
<td>26.8</td>
<td>23.5</td>
</tr>
<tr>
<td>Parameter</td>
<td>Pre-Dose</td>
<td>20 Min</td>
<td>1 Hour</td>
<td>2 Hours</td>
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<tr>
<td>-------------</td>
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<tr>
<td><strong>Subject 1</strong></td>
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<tr>
<td>Temp °C</td>
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<td>36.5</td>
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<td>115/90</td>
<td>115/85</td>
<td>110/80</td>
<td>120/75</td>
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<td>Pulse/min</td>
<td>84</td>
<td>82</td>
<td>88</td>
<td>80</td>
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<tr>
<td>Temp °C</td>
<td>36.9</td>
<td>36.9</td>
<td>36.9</td>
<td>36.4</td>
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<tr>
<td>BP mm Hg</td>
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<tr>
<td>Pulse/min</td>
<td>80</td>
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<td>84</td>
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<td><strong>Subject 3</strong></td>
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<td></td>
</tr>
<tr>
<td>Temp °C</td>
<td>36.5</td>
<td>36.7</td>
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<tr>
<td>BP mm Hg</td>
<td>100/50</td>
<td>130/70</td>
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<tr>
<td>Pulse/min</td>
<td>60</td>
<td>64</td>
<td>76</td>
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<td><strong>Subject 4</strong></td>
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</tr>
<tr>
<td>Temp °C</td>
<td>36.4</td>
<td>37.2</td>
<td>37.2</td>
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<tr>
<td>BP mm Hg</td>
<td>170/105</td>
<td>150/100</td>
<td>170/100</td>
<td>180/100</td>
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<tr>
<td>Pulse/min</td>
<td>76</td>
<td>72</td>
<td>64</td>
<td>72</td>
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TABLE 5.4

PLASMA RECOVERY AND HALF-LIFE OF VIII:C

Lab 1: EBTS Coagulation Laboratory
Lab 2: RIE Haematology Laboratory

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<th>SUBJECT 3</th>
<th>SUBJECT 4</th>
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<td></td>
<td>Lab 1</td>
<td>Lab 2</td>
<td>Lab 1</td>
<td>Lab 2</td>
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<tr>
<td>Recovery (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>from manufacturers potency</td>
<td>85.3</td>
<td>81.8</td>
<td>66.3</td>
<td>51.8</td>
</tr>
<tr>
<td>from local assay</td>
<td>82.2</td>
<td>78.8</td>
<td>71.2</td>
<td>55.7</td>
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<tr>
<td>Half-Life (Hours)</td>
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<tr>
<td>Distribution and elimination (1st) phase</td>
<td>4.8</td>
<td>3.8</td>
<td>6.9</td>
<td>*</td>
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<tr>
<td>Elimination (2nd) phase</td>
<td>11.2</td>
<td>9.3</td>
<td>14.5</td>
<td>15.3</td>
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* No clear bi-phasic behaviour.
**TABLE 5.5**

Comparison of results using the new SN8TS Product (Z8) with those obtained in the same subjects using previous heat treated SN8TS products (NY 68 °C/2h; NY 68 °C/24h)

<table>
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<tr>
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<th>Lab 2</th>
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<td><strong>SUBJECT 1</strong></td>
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<tr>
<td>Z8 (60 °C/72h)</td>
<td>85.6</td>
<td>81.6</td>
<td>91.8</td>
<td>79.7</td>
<td>80.5</td>
<td>84.6</td>
<td>62.0</td>
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<td>11.2</td>
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<td>9.6</td>
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<td>14.6</td>
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<td>NY (68 °C/2h)</td>
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<tr>
<td>NY (68 °C/24h)</td>
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</table>

| **SUBJECT 3** |       |     |       |     |       |     |       |     |       |     |       |     |       |     |       |     |
| Z8 (60 °C/72h) | 85.6 | 81.6| 91.8  | 79.7| 80.5  | 84.6| 62.0  | 84.4| 105.9 | 64.0| 11.2  | 9.3 | 6.7  | 9.6 | 8.6  | 14.6|
| NY (68 °C/2h)  |       |     |       |     |       |     |       |     |       |     |       |     |       |     |       |     |
| NY (68 °C/24h) |       |     |       |     |       |     |       |     |       |     |       |     |       |     |       |     |

* Recovery based on potency assigned by manufacturer
(5.1B)

FIGURE 1B

VIII:C PLASMA PROFILE

SUBJECT 3
Lab 1 ●
Lab 2 ■

TIME AFTER INFUSION (h)

SUBJECT 4
Lab 1 ●
Lab 2 ■

TIME AFTER INFUSION (h)
5.5 VIRUS SAFETY

Until recently, there was no formal clinical evaluation of the virus safety of Z8. However, all patients are regularly monitored for HIV antibody. No HIV seroconversions have been reported since the introduction of Z8. It is noteworthy that the previous products (NY) heated at 68°C for 2 or 24 hours were not implicated in HIV seroconversions, although several batches of NY were later found to have included HIV-positive donations. Careful follow-up of the recipients of 2 such batches revealed that sero-negative patients remained uninfected (Cuthbert et al, 1988 Appendix 2).

One case of NANB Hepatitis has been reported by the Northern Ireland Haemophilia Reference Centre (Appendix 2). However, the patient had also been given SNBTS product NY (heated at 68°C for 24 hours) and two units of red cells. It is considered likely that the transmission of NANB can probably be ascribed to these other blood products. Confirmation of whether or not Z8 is free from risk from transmission of NANB Hepatitis requires regular follow-up of previously untreated patients (PUPs). This study was commenced recently, using a protocol similar to that used for the evaluation of BY manufactured by the Blood Products Laboratory. Plasma ALT data are available from 4 haemophiliacs enrolled in this study using SNBTS Factor VIII product Z8 heated at 68°C for 72 Hours. Data is presented in Appendix 2.

The lack of ALT evaluations in PUPs is very encouraging as is the published observations of Ludlam et al that 5 PUPs who received only Z8 have failed to develop antibodies to Hepatitis C virus (Ludlam et al, 1989).

Patients 1, 3 and 5 have received single donation cryoprecipitate in addition to Z8 while Patient 9 has only ever been treated with Z8. The data shows no abnormal rise in plasma ALT levels in any patient followed up for 3 - 5 months after infusion with Z8. All patients enrolled in the study will be monitored for at least 2 years after the initial Z8 infusion to confirm NANB hepatitis status.

One case of Hepatitis B infectivity has also been reported. As can be seen from the enclosed correspondence (Appendix 2), the Hepatitis B was diagnosed on 18.03.88. Unfortunately, the previous negative sample was taken on 26.06.87 and so the precise date of the onset of infection is not known. The serological markers found on 18.03.88 suggest an acute infection, with the infective event probably occurring during the preceding 6 months. This would implicate five batches of Z8, each of which were heated at 75°C for 72 hours. However, it is possible he became infected as early as April 1987. (The incubation period of Hepatitis B infection is of the order of 3 months. Thus, infection could have occurred up to 3 months before the last negative sample). This could implicate several more batches of Z8 and two batches of SNBTS Factor VIII NY heated at 68°C for 24 hours. No other cases of Hepatitis B have been reported from any other recipients of any of the implicated batches, although many patients were not immune to Hepatitis B virus at the time these batches were administered.
In conclusion, Z8 has not transmitted HIV. It may have transmitted Hepatitis B when heated at 75°C. However, it is clear that our data on Hepatitis B and Hepatitis NAN8 is of an anecdotal nature and the risk of transmission of such viruses by Z8 heated at 80°C for 72 Hours is currently under assessment in a study using PUP patients.
APPENDIX 1

Clinical Effectiveness
7 October 1987

To: RTD's/Dr W M McClelland

Dear

LICENCE VARIATION – FACTOR VIII – Z8

I am about to submit a product licence variation for this product and it is necessary that I provide at least a summary of clinical experience of the product to date.

Accordingly I would be grateful if you could:

(a) Confirm that you have had no reports of adverse reactions to Z8.

(b) Provide me with the number of haemophilia A patients treated in your region with Z8 and for how long.

Sorry to trouble you with this information but we do not have it on file.

With kind regards

Yours sincerely

DR R J PERRY
Director
NORTH OF SCOTLAND BLOOD TRANSFUSION SERVICE

Regional Director:
DR W. WHITROW

Regional Donor Organiser:
MRS MARIANNE MACDONALD

Deputy R.D.O.:
MRS ALISON CURTIS

Our Ref: WW/LA

15 October 1987

Dr R J Perry
Director
Protein Fractionation Centre
Ellen's Glen Road
EDINBURGH
EH17 7QT

Dear Bob

LICENCE VARIATION - FACTOR VIII - ZS

Thank you for your letter of October 7 requiring further information on the above product.

(a) I confirm that we have had no reports of adverse reactions.

(b) Batch 0301/70290. We know of one patient who has received 80 vials of this material starting June 30 1987. 80 vials were sent to Wick and we believe they are being used on 2 patients from July 20. 10 vials were sent to Stornoway July 27 and we believe they are being used by 1 patient.

Batch 030/70490. We know of 6 named patients who have received this material all from mid July 87. In addition there are another 2 patients at Wick whom we believe have already received this batch.

Yours sincerely

W Whitrow
Regional Director

PLEASE GIVE BLOOD

Dr. R.J. Crawford,
Consultant,
Glasgow and West of Scotland Blood Transfusion Service,
Law Hospital,
Carluke,
Lanarkshire ML8 5ES.

Dear Bob,

Thank you for your letter of 3rd November, 1987 concerning Licence of the Factor VIII product “28”.

Most of our regularly treated haemophiliacs appear to have received this product since its introduction in April-May, 1987 and it is our impression in the haemophilia unit that there is no increased incidence of transfusion reactions. Dr. Davidson is also writing to you concerning the numbers of haemophiliacs who have received this product.

Kind Regards.

Yours sincerely,

[Signature]

Dr. G.D.O. Lowe,
Senior Lecturer in Medicine.

cc Dr. J.F. Davidson,
Department of Haematology,
Glasgow Royal Infirmary.

Dr. B. Gibson,
Department of Haematology,
R.H.S.C.
15 October 1987

Dr R J Perry
Director
PFC
Ellen's Glen Road
Edinburgh

Dear Bob

Re: LICENCE VARIATION - FACTOR VIII - Z8

I am replying on Brian's behalf to your letter to him of the 7th of October.

Clinical trials of the five patients with Z8 were conducted, as you know, in March and April of 1987, and Z8 was introduced into general use from May.

A total of 44 patients have now received the product and clinical responses appear to be satisfactory.

You will be aware that there is one patient who regularly has an adverse reaction to Z8. He also reacts adversely to NY. I have already asked Christopher for details and I am sure they will be forthcoming for your general information, but my understanding is that he regularly experiences pyrexia and rigors on receiving Z8. He has been exclusively treated with 8Y from England for the last 2 months without any adverse reactions.

I hope this information is helpful; please let me know if you need to have any further details.

Kindest regards.

Yours sincerely

[Signature]

F E BOULTON
Deputy Director

cc Dr D B L McClelland
EMB/AMR/17.8

2nd November 1987

Dr. R. J. Perry,
Director,
Protein Fractionation Centre,
Scottish National Blood Transfusion Service,
Ellen's Glen Road,
Edinburgh EH17 7CT

Dear Bob,

**LICENCE VARIATION - FACTOR VIII - Z8**

In reply to your letter of 7th October

a. I have received no reports of adverse reactions to Z8.

b. Z8 was first introduced to this Centre in early August 1987. We have received two batches to date and they have been distributed to 10 patients. Nine of these are on long-term, regular, frequent use home treatment and have received between 10 and 130 vials.

The last is a little boy who is a frequent visitor to our Region and he has so far received 8 vials.

In summary, it has been used with no problems.

Yours sincerely,

Dr. Ewa M. Brookes
Regional Director
SJU/am

Dr R J Perry
SNBTS
Protein Fractionation Centre
Ellen's Glen Road
EDINBURGH
EH17 7QT

Dear Bob

With regard to your letter of 7 October 1987, I confirm that we have had no known reactions to Z8 Factor VIII which has been used since May 1987, and has been given to 9 haemophiliacs in this region.

I hope this is what you require.

Kind regards

Yours sincerely

Dr S J Urbaniak
Regional Director

20 October 1987
10 November 1987

Dr R Crawford
Consultant
BTS
Law Hospital
Carluke

Dear Dr Crawford

We have 20 boys at Royal Hospital for Sick Children, who have received Z8 and there have been no reactions reported. We have used Z8 since June of this year. Many of our mothers report that they have to give more Z8 Factor VIII than the previous product to get the same clinical effect. The increase appears to be as high as 30-40% in some cases.

Yours sincerely

BRENDA GIBSON
CONSULTANT HAEMATOLOGIST
HAEMATOLOGY DEPARTMENT

30 December 1987

Dr Crawford
Consultant
BTS
Law Hospital
Carluke

Dear Bob

re: Z8

I can give you the following replies:

a  I cannot give you batch numbers, but can say that our impression is that all batches of Z8 have been incriminated.

b  Infusion is calculated by unitage and then rounded up to the nearest number of bottles by the staff. The parents would then be told the number of bottles to give for each type of blood.

c  I do not have documentation in terms of post-transfusion levels. Many of these patients are HIV positive and are on home therapy and therefore rarely receive treatment in hospital.

I hope these comments are of some help.

Yours sincerely

Brenda Gibson
Consultant Haematologist
APPENDIX 2

Case Correspondence And PUP Data
PROTEIN FRACTIONATION CENTRE

ADVERSE REACTION REPORT

PRODUCT TYPE: \( \text{\textit{L}} \) (28 + \text{\textit{R}})

BATCH NUMBER: 4 Batches in total - see over

DATE INITIATED: 1/2/88

SUMMARY OF ACTION TAKEN

SEE REPORT OVER

REPORT COMPILED BY: S. C. Mitchell
(SIGN) 12/5/88

REPORT CIRCULATED TO:

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<tr>
<td>LABORATORY MANAGER</td>
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AND THEN FILE
PROTEIN FRACTIONATION CENTRE

ADVERSE REACTION REPORT

NON-A, NON-B HEPATITIS AFTER FVIII THERAPY

Non-A, Non-B Hepatitis was reported in a mild haemophilic who received FVIII therapy from 25 September to 7 October. Full details are contained in the appended report from Dr Dempsey. The batches implicated are as follows:-

a. FVIII (NY) Heated 68°C/24h
   Batch 3402-60100 7201u
   3409-56470 8001u

b. FVIII (Z8)
   Batch 0302-70350 9.8001u Heated 80°C/72h
   0304-70550 15.6001u Heated 75°C/72h

c. Whole Blood
   Two units

ACTION TAKEN

1. Full correspondence with Dr Dempsey appended.
2. Action taken to set aside product heated at 80°C for future therapy of
   virgin/mild haemophiliacs.
3. Batch files and card index of infectious events fully annotated.
4. Although FVIII NY was heated at 68°C for 24 hours, it was considered
   unlikely that this would inactivate NAN8 Hepatitis. As this patient
   received NY, it was considered that this was the most likely cause of
   the NAN8 Hepatitis. For this reason, no follow-up has been made of
   the other recipients of the batches of Z8. Similarly, it was not
   considered necessary to report this incident to the OHSS.

B CUTHBERTSON
3.5.88

(SMC02601.058)
25 March 1988

Dr S I Dempsey
Consultant Haematologist
The Royal Belfast Hospital for Sick Children
BELFAST
BT12 8BE
Northern Ireland

Dear Dr Dempsey,

Very many thanks for your comprehensive report regarding NANB transmitted to the above patient. My main concern was to establish whether or not our new product (Z8) which was heated to 80°/72hrs (most recently 75°C) had transmitted NANB since it is our expectation that this material is 'non-infective' for HB, NANB and HIV. I am heartened by your report since it is now clear that the NANB was probably due to infusions of our earlier product batches 340260100 and 340950470 which would only have been heated at 68° for 24 hrs and probably not free of the risk of NANB transmission. Also I note that two units of red cells were infused and these may have been the cause of transmission.

In the light of your full report, I do not need any further information and I will take no further action.

I presume that our old generation product has now been consumed and so for the future any similar patients (mild or virgin) can be treated exclusively with our new generation Z8 product which carries a much lower risk of virus (NANB) transmission.

Very many thanks for your assistance.

With kind regards

Yours sincerely

DR R J PERRY
Director

cc Dr Eliz E Mayne, Dr M McClelland

IMR14102.038
25 March 1988

Dr F Boulton
Edinburgh and South-East Scotland
Blood Transfusion Service
Royal Infirmary
EDINBURGH
EH3 9H8

Dear F Boulton

28 - NANB IN NORTHERN IRELAND

The enclosed correspondence is self-explanatory - unfortunate that the boy was unnecessarily exposed to 68's material (MY). However, clearly there is no reason to implicate 28 in this case of NANB transmission and therefore no need to visit Belfast.

Many thanks for your offer anyway.

With kind regards

Yours sincerely

DR R J PERRY
Director

Enc
15 March 1988

Dr R J Perry
Director
Scottish National Blood Transfusion Service
Protein Fractionation Centre
21 Ellen’s Glen Road
EDINBURGH EH17 7QT

Dear Dr Perry

Thank you for your recent letter regarding our patient here who has recently jaundiced following Factor VIII therapy.

He was a mildly affected haemophiliac who has little in the way of problems as a rule. He was admitted to the ward on the 25th September of last year having sustained an injury to his right thigh. He developed a very large haematoma as a result. He was in the ward and received Factor VIII therapy initially three times a day until his discharge home on the 7th October 1987. The boy is currently 15 years of age. He had not had any Factor VIII since October 1981. He has not required further Factor VIII since his discharge from hospital on the 7th October 1987. During his stay in hospital and following his discharge the haematoma in his right thigh resolved satisfactorily.

He was seen for review on the 28th October when he had been unwell over the previous week. He had been rather lethargic and shivery. He had not been eating. There had been no associated vomiting, nausea or diarrhoea. On examination he appeared to be slightly jaundiced. His liver was enlarged two to three fingerbreadths and was tender on palpation. Investigations on the 28th October showed a bilirubin level of 56 mmol/l. The AST was recorded as 620 u/l and the ALT 1335 u/l. The boy was seen again for review on the 2nd November when he was very much better. His liver was no longer tender or palpable. Further investigations then showed a bilirubin of 10 mmol/l, AST 43 u/l, ALT 252 u/l. He was seen again on the 19th November when the bilirubin level was recorded as <17 mmol/l, the AST 26 u/l and the ALT 25 u/l. He is now healthy and well back at school and there appears to be no residual problem.

In relation to the questions you asked:

a) Details of his exposure to other batches before or since.

b) Details of any other blood products administered.

The boy was transfused with two units of packed cells during his admission and we have a record of these.

c) Details of the implicated batches administered.

These are as follows:

340260100 720 units;
340950470 800 units;

cont...
The Royal Belfast Hospital
for Sick Children
Belfast BT12 6BE Northern Ireland. telephone 240503

Dr R J Parry
Re: 

030470550 15,600 units;
030270350 9,800 units.
d) Details of the illness.
For details of the illness and liver function tests see above. The following
serological investigations were carried out. At the time of his presentation
with the episode of jaundice was HBSAG negative anti HAV IgM negative.
On the 2nd November a sample was taken and he was noted to be both CMV negative
and anti EBV IgM negative. A further sample was obtained on the 15th January
and the boy remains HBSAG negative and HIV negative. Serology for CMV and
EB virus have not been rechecked. We have not tested for hepatitis delta.
e) Details of any ongoing investigations.
We are not awaiting results of any further investigations on this boy.

I hope that this letter answers most of your queries about this episode. From the
results it does look like a case of non A nonB hepatitis.

If I can be of any further help please let me know.

Yours sincerely

[Signature]

S I DEMPSEY
Consultant Haematologist
23 February 1988

Dr F E Boulton
Edinburgh and South-East Scotland
Blood Transfusion Service
Royal Infirmary
EDINBURGH
EH3 9H8

Dear Frank,

NANB HEPATITIS FROM Z8-030270350

I have just received the enclosed from Dr Wayne. I have sent the enclosed letter seeking further information but cannot escape the conclusion that we must visit and discuss the case history in detail to establish whether or not there is an unequivocal causal relationship between this batch and the clinical jaundice (the batch was 80°C heated and there are no abnormal/unusual batch features). I hope you can agree to visit Northern Ireland with either myself or Bruce Cuthbertson. I will let Morris McClelland know of my plans.

With kind regards

Yours sincerely

DR R J PERRY
Director

Enc
18 February 1988

Dr R.J. Perry
Director
Scottish National Blood Transfusion Service
Protein Fractionation Centre
Ellen's Glen Road
Edinburgh
EH17 7QT

Dear Dr Perry

Morris McClelland, many months ago, asked me to provide you with information regarding Factor VIII-Z8. Treatment commenced shortly after receipt of Factor Z8 in July of last year. To date some 28 patients have been treated on many occasions with 7 batches. There has only been one adverse clinical reaction. One patient in the Children's Hospital received Batch No. 030270350 on 29th and 30th September, 1987. I understand from Dr Dempsey, the Haematologist in charge of the children's treatment, that he subsequently a few weeks later developed clinical jaundice and blood results in keeping with non-A non-B hepatitis. He has duly documented this on the normal hepatitis survey form for the Oxford Haemophilia Centre. I have not yet received my copy of the information but I feel that he is satisfied that it was a clearcut episode of hepatitis with no other cause for it and all other tests being negative.

The patients are very pleased with the Z8, as there is increased unitage per bottle, because at the old level of 160 units per bottle it was very difficult to maintain Home Treatment for some of the very heavy weight or perhaps overweight haemophilic patients of greater than 90 kilos. I also hear from the patients that it is more readily soluble and they feel they are getting more adequate dosage.

I apologise for this information being so delayed and indeed it may be too late to provide you with the clinical experience necessary for submission for a product licence. There was some difficulty with the computer in or around the Christmas period and again I apologise for the tardy nature of this information.

With many thanks for all your help.

Yours sincerely,

Elizabeth E. Mayne
Consultant Haematologist
Our Ref: rjp/bc/lab 28 Licence Applicat-

22 February 1988

Dr Elizabeth E Mayne
Consultant Haematologist
Eastern Health & Social Services Board
Royal Victoria Hospital
Belfast BT12 6BA

Dear Dr Mayne

NANB HEPATITIS AND Z8 BATCH 0302 - 70350

Thank you for your letter of 16 February. I was pleased to hear that adverse reactions have been rare and that you are pleased with the general characteristics of the Z8 product.

I was, however, rather concerned to hear of a possible case of NANB Hepatitis in a recipient of batch 0302 - 70350. Because our objective is to produce a non-infective product, you will understand that we need to obtain as full a report as possible to permit us to make a definitive conclusion on whether this can be confirmed as a case of product-mediated infection. I note that you are still waiting for the report from Dr Dempsey, I wonder if you can try to persuade him to supply his report in the near future. We would be particularly interested to know the following:

a) Details of his exposure to other batches before or since.

b) Details of any other blood products administered.

c) Dose of the implicated batch administered on 29 and 30 September.

d) Details of the NANB - Date of onset.
   - Details of the serological investigation. Has he been checked for CMV, EB, Hepatitis A, Hepatitis B Hepatitis Delta.
   - Details of ALT/AST investigations.

e) Details of any on-going investigations.

RJP/BC/LAB.8802221.LTR002
In addition to your written report I think it would be important for myself or Dr. Cuthbertson (Quality Assurance Manager) and Dr. Frank Boulton to visit you and discuss the details in person.

I look forward to hearing from you.

With many thanks for your help.

Yours sincerely

DR R J FERRY
Director

cc. Dr M McClelland
   Dr S I Dempsey
   Dr F E Boulton
   Prof J D Cash
   Dr B Cuthbertson

Ps. I would be grateful if you could let me have a copy of the report sent to the Oxford Haemophilia Centre by Dr. Dempsey.
11 April 1988

Dr. R. J. Perry
Director
Scottish National Blood Transfusion Service
Protein Fractionation Centre
Ellen's Glen Road
Edinburgh EH17 7QT

re: Z3 and Hepatitis

Dear Dr. Perry

I am delighted with the information obtained from Dr. Dempsey which indicates that the non-A non-B hepatitis could have been transmitted in infusions of the earlier batch numbers with the lower heat treatment period. I am sure you were relieved at this information and the good record of Z3 continues.

With kind regards,

Yours sincerely,

E. E. Mayne
Consultant Haematologist

/pro
PLASMA ALT LEVELS FROM PATIENT 1 (PART PUP) RECEIVING SNBTS FACTOR VIII PRODUCT Z8

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<th>DATE</th>
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</table>

* Z8 Batch 81680 Infused from 22 December 1988 to 24 December 1988
Z8 Batch 81723 Infused from 26 December 1988 to 1 January 1989

* NOTE: THIS PATIENT HAD PREVIOUSLY RECEIVED 3 UNITS OF SINGLE DONOR CRYOPRECIPITATE.
PLASMA ALT LEVELS FROM PATIENT 3 (PART PUP) RECEIVING SNBTS FACTOR VIII PRODUCT Z8

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<tr>
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<td>31</td>
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* Z8 Batch 81770 Infused From 31 January 1989 to 3 February 1989

**NOTE:** THIS PATIENT HAD PREVIOUSLY RECEIVED 14 UNITS OF SINGLE DONOR CRYOPRECIPITATE.
PLASMA ALT LEVELS FROM PATIENT 5 (PART PUP) RECEIVING
SNBTS FACTOR VIII PRODUCT Z8

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* Z8 Batch 70910 Infused 14 February 1989

+ NOTE: THIS PATIENT HAD PREVIOUSLY RECEIVED 4 UNITS OF SINGLE DONOR CRYOPRECIPITATE.
PLASMA ALT LEVELS FROM PATIENT 9 (PUP) RECEIVING
SNBTS FACTOR VIII PRODUCT Z8

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* Z8 Batch 81500 Infused From 11 August 1988 to 17 August 1988
Z8 Batch 81520 Infused From 18 August 1988 to 19 August 1988

(LICENCE APPLICATION : FVIII/Z8) 74
HEPATITIS B CASE CORRESPONDENCE
PROTEIN FRACTIONATION CENTRE

ADVERSE REACTION REPORT

HEPATITIS B INFECTION IN A RECIPIENT OF SNBTS FVIII

1. Summary of Incident

On 28th March 1988, we were advised by Dr Myrtle Peterkin of a case of Hepatitis B infection in a boy with Haemophilia A who was treated with SNBTS FVIII. In the letter Dr Peterkin listed five batches of Z8 which had been administered in the preceding 6 months. Details of these batches are as follows:

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<th>BATCH NUMBER</th>
<th>HEATING CONDITIONS</th>
<th>DISTRIBUTION</th>
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<td>0310 - 70560</td>
<td>75 °C / 72 hours</td>
<td>Glasgow &amp; W. of Scotland BTS</td>
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<tr>
<td>0308 - 70780</td>
<td>75 °C / 72 hours</td>
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<td>0308 - 70810</td>
<td>75 °C / 72 hours</td>
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<td>0309 - 70860</td>
<td>75 °C / 72 hours</td>
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<td>0311 - 71030</td>
<td>75 °C / 72 hours</td>
<td>Glasgow &amp; W. of Scotland BTS</td>
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The Director of the North of Ireland BTS and the North of Scotland BTS were both advised that they had received one of the implicated batches. Both reported that no infective incidents had occurred.

In a later letter dated 5th May 1988, Dr Peterkin advised that the patient had HBsAg on 18/3/88 but no Hepatitis B markers on the previous sample taken on 26/6/87. Thus, the infective incident could have occurred at any time in the previous 9 months. During this period, the patient received many different products, as follows:

1 Batch FVIII NY Heated at 68 °C / 24 hours
4 Batches FVIII Z8 Heated at 80 °C / 72 hours
6 Batches FVIII Z8 Heated at 75 °C / 72 hours

Theoretically, any one of these 11 batches could have been implicated. However, the presence of IgM in the sample taken on 18.3.88 strongly suggests that the infection occurred in the preceding 6 months, as suggested in Dr Peterkin's original letter.

(LICENCE APPLICATION : FVIII/28)

76
In conclusion, this infection probably occurred in the preceding six months, implicating one of five batches of Z8 heated at 75°C for 72 hours. No other similar cases of Hepatitis B infection have been reported from a recipient of these or any other batches.

2. **Action Taken**

2.1 Other Centres which received common batches advised (see above).

2.2 Batch records annotated with relevant information.

2.3 Card index of infection incidents updated.

2.4 The DHSS were not advised as this was considered an expected risk of receiving FVIII heated only at 75°C.

DR B CUTHBERTSON

20/7/99
28 March 1988

Dr Bruce Cuthbertson
Quality Assurance Manager
SNBTS
Protein Fractionation Centre
Ellen’s Glen Road
EDINBURGH

Dear Dr Cuthbertson

ALLEGED TRANSFUSION TRANSMITTED HEPATITIS B INFECTION

We have just had a report of a case of alleged transfusion transmitted hepatitis B in a boy with Haemophilia A.

We have been assured that he has never received any commercial FVIII and has had no transfusions of blood or other blood products. His mother was specifically questioned about the possibility of any high risk activity and denies this. She was tested on 25.3.88 and found to be HBsAg negative. The lad has received several batches of FVIII in the past 6 months, the ones which may be suspect are:

0309-70780 0309-70810 0309-70860 0310-70560 0311-71030

The hospital at which he is being followed is checking other recipients of these batches to see if any other patients have seroconverted. We'll let you know the outcome of their investigations. We would be happy to know if you turn up anything of interest in any of this material.

Yours sincerely,

Myrtle Paterson
Senior Registrar

PS Do you think you can chase up that vial of anti-D you promised to send me? We were hoping to do some tests on it before the Easter holidays.
Scottish National Blood Transfusion Association
PROTEIN FRACTIONATION CENTRE
Ellen's Glen Road, Edinburgh EH17 7QT

PLASMA FRACTION—BATCH ISSUE HISTORY

**Product:** FVIII concentrate 28
**Batch No.:** 03/11-710.32

Date placed at issue: 13/1/88

**Authorised for issue:**

**Expiration Date:** 13/1/88

No. units placed at issue: 6/6
Unit Size: 20mL

**Breakages etc.:**

Biological Value: 150 IU

**Date issue Complete:** 13/1/88
Total No. Issued: 6/6

Issue data correct: Yes

**Date issued** | **No. issued** | **Receiving Centre** |
---|---|---|
13/1/88 | 6/6 | GLP

Date checked: 13/1/88

Wescott & Co. Ltd. 1982 A.G. 19
**Scottish National Blood Transfusion Association**  
**PROTEIN FRACTIONATION CENTRE**  
Ellen's Glen Road, Edinburgh EH17 7QT

---

**PLASMA FRACTION—BATCH ISSUE HISTORY**

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**Authorised for issue:**  
**Date placed at issue:** 21/7/87

**Expiry Date:** 23/12/87

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**Breakages etc.:**  
**Date issue Complete:** 23.12.87  
**Total No. Issued:** 448

**Issue data correct:**  
**Date checked:** 23.12.87

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| 23.12.87 | 448 | GLA

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*Woods & Co. Ltd. 15/17/18 K.C.C. 19*
Scottish National Blood Transfusion Association
PROTEIN FRACTIONATION CENTRE
Ellen’s Glen Road, Edinburgh EH17 7QT

PLASMA FRACTION—BATCH ISSUE HISTORY

Product: FACTOR VIII CONC (28)  
Batch No.: 0309-70560

Authorised for issue: (Signature)  
Date placed at issue: 30/11/87

Expiry Date: 22/7/87

No. units placed at issue: 709  
Unit Size: 20ml  
Biological Value: 230 I.U.

Breakages etc.:  
Date issue Complete: 2.12.87  
Total No. Issued: 709

Issue data correct: (Signature)  
Date checked: 2.12.87

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Wells & Co. Ltd. 17/07/78 7.12.87
Scottish National Blood Transfusion Association
PROTEIN FRACTIONATION CENTRE
Ellen's Glen Road, Edinburgh EH17 7QT

PLASMA FRACTION—BATCH ISSUE HISTORY

Product: 20L 1/8th 60mls J.H.T. 2x
Batch No.: 2355-76610

Authorised for issue: G. Cartwright
Date placed at issue: 2/1/82

Expiry Date: 3/1/92

No. units placed at issue: 497
Unit Size: 25 ml

Breakages etc.: 

Date issue Complete: 5/11/82
Total No. Issued: 697

Issue data correct: 

Date No. issued Receiving Centre Date No. issued Receiving Centre
1/1/82 400 Bel d.L.
5/11/82 297 C.L. A.L.
Scottish National Blood Transfusion Association
PROTEIN FRACTIONATION CENTRE
Ellen's Glen Road, Edinburgh EH17 7QT

PLASMA FRACTION—BATCH ISSUE HISTORY

Product: Fuolinolone
Batch No.: 036-74756

Authorised for issue: [Signature]
Date placed at issue: 14/10/10

Expiry Date: 14/10/95

No. units placed at issue: 655
Unit Size: 20 ml

Breakages: [Blank]
Date issued: 14/10/10

Biological Value: 25

Total No. Issued: 655

Issue data correct: [Signature]
Date checked: 14/10/10

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[Signature]
Our Ref: bc/lab

14 April 1988

Dr M Petarkin
Senior Registrar
Glasgow & West of Scotland
Blood Transfusion Service
Lay Hospital
Carluke
Lanarkshire ML8 8ES

Dear Myrtle

HEPATITIS B INFECTION AND FVIII (Z8)

Thank you for your letter of 29 March, advising us of a case of Hepatitis B in a boy with haemophillia A. I have checked through our files and can offer no information which assists in your investigation:

- No reports have been received which would suggest that any of the donations used any of the six batches have been implicated in Hepatitis B transmission.

- No other reports of Hepatitis B transmission have been received from other Centres receiving any of these batches.

209 vials of 0309 – 70850 went to Inverness
400 vials of 0305 – 70810 went to Belfast

I have written to Dr McClelland and Dr Whitrow, asking them to confirm that no cases of Hepatitis B have occurred.

- All 6 batches had been heated at 75°C for 72 h.

As there are 6 batches implicated, it is clearly unreasonable to ask Regional Centres to recheck the constituent donations. This might become a realistic undertaking if we can reduce the numbers of implicated batches.

I am sure that you are still investigating the incident and look forward to receiving your report. The information that would particularly interest me is as follows:

BC/LAB. 880414. LT9003

84
Dr M Peterkin

Dr M Peterkin

a. Sequential Hepatitis B serology data.
b. Likely dates when infection could have occurred.
c. Dosages of each batch used and dates administered.
d. Whether he had been vaccinated for Hepatitis B.
e. How many non-immune patients are being treated in the West of Scotland.

I shall advise you if any further information comes to light at this end.

With many thanks for your report.

Yours sincerely

Dr B CUTHBERTSON
Quality Assurance Manager
5 May 1988

Dr B Cuthbertson
SNBTS
Protein Fractionation Centre
Ellen's Glen Road
EDINBURGH

Dear Dr Cuthbertson

HEPATITIS B INFECTION AND FVIII (Z8)

Thank you for your letter of 14 April 1988. The delay in replying is due to the fact that the information you asked for relating to FVIII dosage is very difficult to come by for patients, like this young boy, who are on home treatment. We’re had to wait until he attended the clinic to get hold of the treatment diary his mother keeps. A photocopy of his treatment over the past year is enclosed.

The other information you required is:

1 Sequential Hepatitis B Serology (Regional Virus Laboratory, Ruchill Hospital)

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<tr>
<th>Date of Specimen</th>
<th>3/4/87</th>
<th>26/6/87</th>
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<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>Pos</td>
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<tr>
<td>Anti HBs</td>
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<td>NT</td>
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<tr>
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<td>Neg</td>
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<td>NT</td>
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<td>Pos</td>
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<td>HBeAg</td>
<td>NT</td>
<td>NT</td>
<td>Pos</td>
<td>Pos</td>
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</tbody>
</table>

NT = Not Tested

From the above, this lad’s infection was acquired sometime between 26/6/87 and 18/3/88. Unfortunately a specimen allegedly taken on 4/12/87 never reached the Regional Virus Lab so we cannot define the time of infection more precisely.

2 Active Immunisation

4/2/88 First dose ENGERIX B administered
18/3/88 Second dose ENGERIX B

3 I’ve been informed by the staff at the Royal Hospital for Sick Children, Glasgow that they are currently treating 25 non-immune haemophiliacs, 19 of whom have completed a full course of active immunisation, the others have received 1 or 2 vaccine doses. Four haemophiliacs are immune.
5 May 1988

Dr B Cuthbertson

I hope this is helpful.

With best wishes.

Yours sincerely,

[Signature]

Myrtle Peterkin
Senior Registrar

Enc
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<td>6 60</td>
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<td>0302-70370</td>
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Our Ref: 961/96

14 April 1988

Dr W M McClelland
Northern Ireland Blood Transfusion Service
89 Orphan Street
BELFAST BT12 6GE

Dear Morris

HEPATITIS B IN A RECIPIENT OF ZS

I enclose a copy of a letter from Dr Myrtle Peterkin, advising of a suspected case of Hepatitis B in a West of Scotland BTS patient. You will note that 18 batches are implicated. 400 vials of batch 0305 - 70810 were sent to Northern Ireland on 1.12.87. I wonder if you can advise me of the following:

a. Are your local haemophiliacs all vaccinated against Hepatitis B?

b. Are they routinely checked for HBSAg?

c. Is there any evidence to implicate this batch in any other cases of Hepatitis B transmission.

With many thanks, once again for your help.

Yours sincerely

DR B CUTHBERTSON
Quality Assurance Manager

Encl

8C/LA8.880414.LTR000
The Royal Belfast Hospital for Sick Children
Belfast BT12 6BE Northern Ireland. telephone [redacted]

1 June 1988

Dr B Cuthbertson
Quality Assurance Manager
Scottish National Blood Transfusion Service
Protein Fractionation Centre
Ellen's Glen Road
Edinburgh
EH17 7QT

Dear Dr Cuthbertson

Re: Hepatitis B in a Recipient of Z8

Thank you for your recent letter which Dr. Elizabeth Mayne, Consultant Haematologist in the Royal Victoria Hospital has passed on to me. In your letter you ask a number of questions. All our haemophiliacs are currently checked routinely for HbsAg. None are currently positive. We have not yet instituted a vaccination programme against Hepatitis B. We are now however getting this underway. As yet we have no evidence to indicate batch No. 0305 -70810 in any Hepatitis B cases here. If I can be of any further assistance please let me know.

Yours sincerely

[Signature]

S I Dempsey
Consultant Haematologist

---

PROTEIN FRACTIONATION CENTRE

Received: 6/6/88

File No: [redacted]

Refer to: [redacted]

Action taken: [redacted]
24 May 1988

Dr. B. Cuthbertson
Quality Assurance Manager
Scottish National Blood Transfusion Service
Protein Fractionation Centre
Ellen's Glen Road
Edinburgh EH17 7QT

re: Hepatitis B in a Recipient of Z8

Dear Dr. Cuthbertson,

Dr. McClelland has passed on your letter to me regarding the hepatitis B in a recipient of Z8. I have sent this letter on to Dr. Dempsey, as he is responsible for the management of all paediatric haemophiliacs. I think he organises any vaccination for them. They are all routinely checked for HbsAg and I have no knowledge of any evidence to implicate this batch in cases of hepatitis B.

Yours sincerely,

E. E. Mayne
Consultant Haematologist

a.c. Dr. S.I. Dempsey, RBHSC

/ap
Scottish National Blood Transfusion Service
Protein Fractionation Centre,
Ellen's Glen Road,
Edinburgh,
EH17 7QT

Director:
Dr. R. J. Perry

Our Ref: bc/lab

14 April 1988

Dr W Whitrow
North Of Scotland Blood Transfusion Service
Raigmore Hospital
INVERNESS IV2 3UJ

Dear Bill

HEPATITIS B IN A RECIPIENT OF Z8

I enclose a copy of a letter from Dr Myrtle Peterkin, advising of a suspected case of Hepatitis B in a West of Scotland BIS patient. You will note that 6 batches are implicated. 209 vials of batch 0309 - 70860 were sent to Inverness on 1.12.87. I wonder if you can advise me of the following:

a. Are your local haemophiliacs all vaccinated against Hepatitis B?
   - Yes

b. Are they routinely checked for HBSAg?

b. Is there any evidence to implicate this batch in any other cases of Hepatitis B transmission?
   - No

With many thanks, once again for your help.

Yours sincerely

Dr B Cuthbertson
Quality Assurance Manager

Encl

bc/lab.8804.142.LTR003

18/4/88
5.6  BIBLIOGRAPHY  CLINICAL  SECTION

CONTENTS


[LICENCE APPLICATION : FVIII/28] 96
31st March 1987

Dr R Perry,
P.F.C.
Ellens Glen Road,
Edinburgh.

Dear Dr Perry

Please find enclosed the latest data on the haemophiliacs infused with Z8-80 trial material. (I have included Adam McGill’s and my own calculations).

1. (volunteer no.1) Results using Diagen substrate.
   - Half life 15 ½ hours
   - Recovery (based on labelled dosage) 74%
   - Recovery (based on assayed dosage) 86%

2. (volunteer no.3)
   - Half life 12 hours
   - Recovery (based on labelled dosage) 66%
   - Recovery (based on assayed dosage) 76%

3. (volunteer no.4)
   - Half life 9 hours
   - Recovery (based on labelled dosage) 81%
   - Recovery (based on assayed dosage) 83%

Dr Chris Prowse will be in touch soon with the Haematology Dept. assay results.

No further infusions are planned until Dr C Ludlam returns from holiday in three weeks time.

Yours sincerely

[Signature]

Dr S P Howe
Weight = 59.5 Kg.
Est PE Vol = 2440

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<td>0.22</td>
<td>0.20</td>
</tr>
<tr>
<td>28</td>
<td>0.14</td>
<td>0.21</td>
<td>0.18</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Extrapolated $T_0$ value = 0.68

Therefore recovery at $T_0 = 1659$ units

\[
= \frac{1659}{2354} = 70\% \text{ of dose}
\]

$T_{1/2} = 13\ h\ 40\ min$
Weight = 74.7 Kg
Est PE Vol = 3063

<table>
<thead>
<tr>
<th>DOSE</th>
<th>VOL.</th>
<th>BTS</th>
<th>HAEM.</th>
<th>MEAN</th>
<th>DIFF.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>233</td>
<td>11.25</td>
<td>11.25</td>
<td>2621</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>9.5</td>
<td>9.5</td>
<td>2213</td>
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<td></td>
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<td></td>
<td>2417</td>
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<table>
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<tr>
<th>Time</th>
<th>BTS</th>
<th>HAEM.</th>
<th>MEAN</th>
<th>DIFF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>0.01</td>
<td>0.01</td>
<td></td>
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</tr>
<tr>
<td>1h</td>
<td>0.66</td>
<td>0.70</td>
<td>0.68</td>
<td>0.68</td>
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<tr>
<td>2h</td>
<td>0.60</td>
<td>0.67</td>
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<tr>
<td>3h</td>
<td>0.54</td>
<td>0.67</td>
<td>0.61</td>
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<tr>
<td>5h</td>
<td>0.44</td>
<td>0.51</td>
<td>0.48</td>
<td>0.48</td>
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<tr>
<td>7h</td>
<td>0.36</td>
<td>0.41</td>
<td>0.39</td>
<td>0.39</td>
</tr>
<tr>
<td>24h</td>
<td>0.09</td>
<td>0.17</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>28h</td>
<td>0.07</td>
<td>0.11</td>
<td>0.09</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Extrapolated $T_o = 0.72$ u/ml
Therefore recovery at $T_o = 0.72 \times 3063 = 2205$ units

$\frac{2205}{2417} = 91\%$ of dose

$T_{1/2} = 9\ h\ 40\ min$
Weight = 68 Kg.
Est. Pe Vol = 2788

<table>
<thead>
<tr>
<th>DOSE</th>
<th>VOL (ml)</th>
<th>BTS</th>
<th>HAEM</th>
<th>MEAN</th>
<th>DIFF.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>227</td>
<td>10.8</td>
<td>2451</td>
<td>2349</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>9.9</td>
<td>2247</td>
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<table>
<thead>
<tr>
<th>Time</th>
<th>BTS</th>
<th>HAEM</th>
<th>MEAN</th>
<th>DIFF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>0.07</td>
<td>0.11</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>1h</td>
<td>0.90</td>
<td>0.83</td>
<td>0.87</td>
<td>0.78</td>
</tr>
<tr>
<td>2h</td>
<td>0.95</td>
<td>0.66</td>
<td>0.81</td>
<td>0.72</td>
</tr>
<tr>
<td>3h</td>
<td>0.72</td>
<td>0.66</td>
<td>0.69</td>
<td>0.60</td>
</tr>
<tr>
<td>5h</td>
<td>0.66</td>
<td>0.61</td>
<td>0.63</td>
<td>0.54</td>
</tr>
<tr>
<td>7h</td>
<td>0.68</td>
<td>0.61</td>
<td>0.62</td>
<td>0.53</td>
</tr>
<tr>
<td>24h</td>
<td>0.23</td>
<td>0.25</td>
<td>0.24</td>
<td>0.15</td>
</tr>
<tr>
<td>28h</td>
<td>0.18</td>
<td>0.24</td>
<td>0.21</td>
<td>0.12</td>
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</tbody>
</table>

Extrapolated T₀ value = 0.80
Therefore recovery at T₀ = 0.80 x 2788 = 2230 units

\[
= \frac{2230}{2349} = 95\% \text{ of dose}
\]

\[ T_{1/2} = 10\text{h}. \]

Note: had received therapy with fum within past 48 hours, hence the way not be fully reliable.
ight = 52 Kg
: Pe Vol = 2132

<table>
<thead>
<tr>
<th>TIME (h)</th>
<th>VOL (ml)</th>
<th>HAEM. ASSAY</th>
<th>BTS ASSAY</th>
<th>MEAN</th>
<th>DIFF.</th>
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<tbody>
<tr>
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<td>0.02</td>
<td>0.04</td>
<td>0.03</td>
<td>-</td>
<td></td>
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<tr>
<td>1h</td>
<td>0.93</td>
<td>0.83</td>
<td>0.88</td>
<td>0.85</td>
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</tr>
<tr>
<td>2h</td>
<td>0.70</td>
<td>0.61</td>
<td>0.66</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>3h</td>
<td>0.72</td>
<td>0.52</td>
<td>0.62</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>5h</td>
<td>0.38</td>
<td>0.47</td>
<td>0.43</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>7h</td>
<td>0.54</td>
<td>0.41</td>
<td>0.42</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>24h</td>
<td>0.06</td>
<td>0.10</td>
<td>0.08</td>
<td>0.05</td>
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</tr>
<tr>
<td>28h</td>
<td>0.05</td>
<td>0.10</td>
<td>0.07</td>
<td>0.04</td>
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</tbody>
</table>

Extrapolated $T_0 = 0.81$

Therefore recovery at $T_0 = 0.81 \times 2132 = 1727$ units

$\frac{1727}{1961} = 88.1\%$ of Dose

$T_2 = 6 \text{ h } 20 \text{ min.}$
Z-8-80 INFUSIONS  (Batch 286-027)
March & April 1987

Recovery are based on 42 ml plasma/kg and measured potency at volume of dx.
Assays are one-stage using O Plasma standard with concentrates
pre-diluted in haemophilic plasma to 1U/ml. Results from
EBIS Coagulation Laboratory + Haematology RIE (Label potency of 2.8-6.027 to 9.7U).

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>SUBSTRATE</th>
<th>Dose</th>
<th>vill. U/ml</th>
<th>0</th>
<th>1h</th>
<th>2h</th>
<th>4h</th>
<th>6h</th>
<th>24h</th>
<th>48h</th>
<th>(%)</th>
<th>(h)</th>
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</thead>
<tbody>
<tr>
<td>(i)</td>
<td>BIS VM</td>
<td>81T</td>
<td>0.02 0.38 0.38 0.34 0.25 0.25 0.20 0.22</td>
<td>70</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>(j)</td>
<td>BIS Diagn</td>
<td>81T</td>
<td>&lt;0.01 0.46 0.50 0.43 0.38 0.35 0.17 0.15</td>
<td>92</td>
<td>16</td>
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<tr>
<td>(k)</td>
<td>Haem Dian</td>
<td>81T</td>
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<td>54</td>
<td>15.5</td>
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<tr>
<td>(l)</td>
<td>BIS Diagn</td>
<td>514</td>
<td>≤0.03 0.35 0.36 0.36 0.34 0.32 0.15 0.15</td>
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<tr>
<td>(m)</td>
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<tr>
<td>(n)</td>
<td>BIS Diagn</td>
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<td>77</td>
<td>14</td>
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<tr>
<td>(o)</td>
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<td>0.02 0.43 0.43 0.43 0.42 0.24 0.15 0.15</td>
<td>59</td>
<td>14</td>
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<tr>
<td>(p)</td>
<td>BIS Dian</td>
<td>514</td>
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<td>12</td>
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<tr>
<td>(q)</td>
<td>Haem Dian</td>
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<td>0.01 0.70 0.59 0.53 0.35 0.32 0.08 0.08</td>
<td>80</td>
<td>8.5</td>
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</tbody>
</table>
FOR THE ATTENTION OF DR R FERRY

FOURTH VOLUNTEER INFUSION OF PFC FACTOR VIII CONCENTRATE 'ZED EIGHT. HEAT TREATED 80 DEGREE C. 72 HOURS BATCH NO. 0312 60270. RECOVERY BASED ON LABELLED DOSAGE 91% RECOVERY BASED ON ASSAYED DOSAGE 83% TWO PHASE DELAY CURVE HALF LIFE 9 HOURS. DISSOLUTION TIME 20-47 MINS (AVERAGE 35) NO SYMPTOMS

WRITTEN REPORT IN POST.

REGARDS

DR B P HOWE
EDINBURGH B.T.S.*
72426 PFCEDI B
72163 BTS EH B
SECOND VOLUNTEER INFUSION OF PFC FACTOR V111 CONCENTRATE 'ZED EIGHT. HEAT TREATED 80°C, 72 HOURS BATCH NO. 0312 60270
RECOVERY BASED ON ASSAYED DOSAGE 55%
RECOVERY BASED ON LABELLED DOSAGE 45%
SINGLE PHASE DECAY CURVE HALF LIFE 10 HOURS
DISSOLUTION TIME 29 & 45 MINS (AGAIN LONG)
NO SYMPTOMS.
WRITTEN REPORT IN THE POST.

ASSAY RESULTS FROM THIRD AND FOURTH PATIENTS LATER THIS WEEK.

S. P. HOWE.φ
72A26 PFCE01 G
72A26 PST6 EH G
FOR THE ATTENTION OF DR. FERRY,

P.F.C.

THIRD VOLUNTEER INFUSION OF PFC FACTOR V111 CONCENTRATE 'ZED EIGHT
HEAT TREATED 90C 72 HOURS BATCH NO. 0312 60270.
RECOVERY BASED ON LABELLED DOSAGE 66%
RECOVERY BASED ON ASSAYED DOSAGE 76%
SINGLE PHASE DECAY CURVE HALF LIFE 12 HOURS
DISSOLUTION TIME 55 MINS (LONGEST YET)
NO SYMPTOMS.

UNABLE TO ASSAY FOURTH VOLUNTEER SAMPLES UNTIL REAGENT DELIVERY
HOWEVER DISSOLUTION TIME 20 - 47 MINS AVERAGE 35 MINS
NO SYMPTOMS.

REPEAT OF FIRST VOLUNTEER ASSAYS USING DIAGEN SUBSTRATE
RECOVERY BASED ON LABELLED DOSAGE 74%
RECOVERY BASED ON ASSAYED DOSAGE 96%
SINGLE PHASE DECAY CURVE HALF LIFE 15 HOURS.

WRITTEN REPORT WILL FOLLOW AFTER FOURTH VOLUNTEER SAMPLES ASSAYED.

S. P. HOWE.
MESSAGE FOR

M. Bob

WHILE YOU WERE OUT

M. Dr. Hence

OF... E0A.RTB

TELEPHONE NO. 229 258J

<table>
<thead>
<tr>
<th>TELEPHONED</th>
<th>PLEASE RING</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALLED TO SEE YOU</td>
<td>WILL CALL AGAIN</td>
</tr>
<tr>
<td>WANTS TO SEE YOU</td>
<td>URGENT</td>
</tr>
</tbody>
</table>

MESSAGE 38 Infarct

Examination didn't agree with haemoglobin results and these are being repeated. Patient night.

M. 38 admitted 12.00 Saturday. The infarct time was 38 minutes. Normally he had no symptoms whatsoever - will have his assessment done next week.

PIO

DATE

TIME

RECEIVED

MESSAGE For

M. 

WHILE YOU WERE OUT

M. 

OF.

TELEPHONE NO.

<table>
<thead>
<tr>
<th>TELEPHONED</th>
<th>PLEASE RING</th>
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</thead>
<tbody>
<tr>
<td>CALLED TO SEE YOU</td>
<td>WILL CALL AGAIN</td>
</tr>
<tr>
<td>WANTS TO SEE YOU</td>
<td>URGENT</td>
</tr>
</tbody>
</table>

MESSAGE Now. No. informed yesterday.

The infarct time was 38 - 47 mins. with an average of 35. No symptoms whatsoever.

Result for the infarct has been completed. The patient will be seen in 3 weeks and will be sent to you as soon as possible and a letter giving the details will be sent to you this week.

DATE 25/1/57 TIME 11.00

RECEIVED
Dear Bob,

Enclosed are the data to hand on haemophilius infused with the 26-80 trial material. We have done 4 infusions as follows:

1) [redacted] - BTS assays with local depleted plasma show discrepancy from Haematology ones with Diapen Substrate. BTS will check by assay with Diapen Substrate.

2) [redacted] BTS assays using Diapen Substrate.

3) [redacted] to be assayed this week. A McGill will send you VIII:C results direct.

Any queries you have on clinical monitoring sheets may be answered by Dr Susan Howe. We will do VIII:C assays when possible.

I understand Glasgow have done 2 or 3 infusions successfully (from Dr Forbes). Your best contact there may be Dr Gordon Lowe in Dept Medicine. For above half-life on (a) 365 looks reasonable, recovery better and hot solubility rather long. Hope this helps - it's all I have at the moment.

Chris Price.
# SNPTS THAT TREATED FACTOR VIII IN VIVO RECOVERY AND LIFE STUDIES NEPHROPHILIA

**Patient's Name**: [Redacted]

**Hospital**: [Redacted]

**D.O.B.**: [Redacted]

**Body Weight**: [Redacted] kg, [Redacted] cm

**Consultant**: [Redacted]

<table>
<thead>
<tr>
<th><strong>Particulars of Infusion</strong></th>
<th><strong>Batch No.</strong></th>
<th><strong>No. of Vials</strong></th>
<th><strong>Volume infused</strong></th>
<th><strong>mLs.</strong></th>
<th><strong>Total dose</strong></th>
</tr>
</thead>
</table>

If local VIII C assay on infusate was performed please give value and also solubility time. Infusion time...

<table>
<thead>
<tr>
<th><strong>Time</strong></th>
<th><strong>Dose Pre</strong></th>
<th><strong>20 min</strong></th>
<th><strong>60 min</strong></th>
<th><strong>120 min</strong></th>
<th><strong>24 h</strong></th>
<th><strong>48 h</strong></th>
<th><strong>72 h</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mLs plasma stored at -20°C</td>
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<td></td>
<td></td>
<td></td>
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</table>

**Temperature**

**Blood Pressure**

**Coag No.**

<table>
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<th>00948</th>
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<th>00951</th>
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**Factor VIII C**

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<th>8.7</th>
<th>0.02</th>
<th>0.46</th>
<th>0.30</th>
<th>0.43</th>
<th>0.38</th>
<th>0.35</th>
<th>0.17</th>
<th>0.18</th>
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</thead>
</table>

**Factor VIII C ag.**

<table>
<thead>
<tr>
<th>Factor VIII C ag.</th>
<th>0.44</th>
<th>0.48</th>
<th>0.41</th>
<th>0.36</th>
<th>0.39</th>
<th>0.15</th>
<th>0.16</th>
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</thead>
</table>

**Factor VIII R**

<table>
<thead>
<tr>
<th>Factor VIII R</th>
<th>[Redacted]</th>
</tr>
</thead>
</table>

**Anti HAE (litre)**

<table>
<thead>
<tr>
<th>Anti HAE (litre)</th>
<th>[Redacted]</th>
</tr>
</thead>
</table>

**10 mL plasma stored at -20°C**

**Notes:**

1. Dose should be infused in 20 minutes.
2. 10 mL plasma should be aliquoted (1 mL) and stored for future studies.
3. Patients selected for this study should be haemostatically stable.
4. Please return completed form to Dr F. Boulton, Edinburgh & South East Blood Transfusion Service.

**Clinical Comments**

---

**Clinical Comments**

---

**SNF 012994**
78.4 Kg x $\pi$ (Plane Vol. ($\text{m}^2$ x $\text{kg}$)) = 3293 m

$\text{Vermiculite} = 0.45$ → 1581 m

$\text{Dose} = 8.75 \text{ m} \times 198 \text{ m} = 1723 \text{ m}$

Recovery = 92%.

$\sqrt{1/2} = 15 \text{ m}$
28 INFUSIONS

VOLUNTEER NO 1

(USING DIAZEPIN)

Recovery (labelled dosage) = $\frac{1478}{1980} = 74\%$

Recovery (assumed dosage) = $\frac{1478}{1722} = 86\%$

$T_\frac{1}{2} = 15\frac{1}{2}$ Hours.

SUSAN HOWE
### SNBTS Heat Treated Factor VIII In Vivo Recovery and Life Studies Haemophilia

**Patient's Name:** [Redacted]  
**Hospital:** [Redacted]  
**D.O.B.:** [Redacted]  
**Body Weight:** 78.4 Kg  
**Height:** 5'5" cm  
**Consultant:** [Redacted]

**Particulars of Infusion:**  
- **Batch No.:** 6312  
- **No. of Vials:** 10  
- **Volume infused:** 19.7 mls  
- **Total dose:** [Redacted]  
- If local VIII C assay on infusate was performed please give value and also value & source of standard.
- **Solubility time:** 3.5 minutes  
- **Infusion time:** 3.5 minutes

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>20&quot;</th>
<th>1hr</th>
<th>2hr</th>
<th>4hr</th>
<th>6hr</th>
<th>8hr</th>
<th>10hr</th>
<th>20hr</th>
<th>30hr</th>
<th>90hr</th>
<th>24hr</th>
<th>48hr</th>
<th>96hr</th>
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<tbody>
<tr>
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<td>37.2</td>
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<td>37.5</td>
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<td>36.9</td>
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<tr>
<td><strong>Blood Pressure</strong></td>
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<td>170/100</td>
<td>160/100</td>
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<tr>
<td><strong>Pulse (bpm)</strong></td>
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<td>64</td>
<td>72</td>
<td>76</td>
<td>74</td>
<td>92</td>
<td>96</td>
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<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td><strong>Factor VIII Cag</strong></td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Factor VIII Rag</strong></td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<td>✔️</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Tests</strong></td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<td>✔️</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of mL allotted</strong></td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>stored at -30°C</strong></td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**  
1. Dose should be infused in 20 minutes.  
2. Save plasma should be aliquoted (1 ml) and stored for future studies.  
3. Patients selected for this study should be haemostatically stable.  
4. Please return completed form to Dr F Boulton, Edinburgh & South East Blood Transfusion Service, Royal Infirmary, Edinburgh.

**Clinical Comments:** Long duration time required, developed arrhythmia after 50% infused.  
**Infection:** No evidence of infection.

SNF.001:2987
**SNPS HEMIAT TREATED FACTOR VIII IN VIVO RECOVERY AND LIFE STUDIES HEMOPHILIA**

**Patient's Name: **[Redacted]

**Hospital:** NC 28

**D.O.B.**

**Body Weight:** Kg. **Height:** cms

**Consultant:**

**Particulars of Infusion:**

<table>
<thead>
<tr>
<th>No. of Vials</th>
<th>Volume infused</th>
<th>Total dose</th>
</tr>
</thead>
</table>

If local VIII C assay on infusion was performed please give value and source of standard.

<table>
<thead>
<tr>
<th>Solubility time</th>
<th>Infusion time</th>
</tr>
</thead>
</table>

### Table

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Blood Pressure</th>
<th>Coag No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.94%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factor VIII C</th>
<th>Factor VIII Cag</th>
<th>Haemostasis VIII C</th>
<th>Anti HB (litres)</th>
<th>10 mls plasma stored at -20°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.7</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.7</td>
<td>0.01</td>
<td>&lt;0.01</td>
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<td>0.7</td>
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<td>&lt;0.01</td>
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</tr>
<tr>
<td>0.7</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
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<tr>
<td>0.7</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Clinical Comments

(1) Dose should be infused in 20 minutes.

(2) 10 mls plasma should be aliquoted (1 ml) and stored for future studies.

(3) Patients selected for this study should be haemostatically stable.

(4) PLEASE RETURN COMPLETED FORM TO DR F BOLTON, EDINBURGH & SOUTH EAST BLOOD TRANSFUSION SERVICE, ROYAL INFIRMARY, EDINBURGH.
# SNBTS: HEAT TREATED FACTOR VIII IN VIVO RECOVERY AND LIFE STUDIES - HAEMOPHILIA

**Patient's Name:** [Redacted]

**Hospital:** D.O.B.: [Redacted]

**Body Weight:** Kg, **Height:** cm

**Consultant:**

---

**Particulars of Infusion:**

- **Batch No.** 60270
- **No. of Vials**
- **Volume infused:** 198 ml
- **Total dose:** 1980

If local VIII C assay on infused was performed please give value and also value & source of standard.

**Solubility time:** minutes

**Infusion time:** minutes

---

<table>
<thead>
<tr>
<th>Dose</th>
<th>Pre</th>
<th>20 Min</th>
<th>60 Min</th>
<th>120 Min</th>
<th>240 Min</th>
<th>360 Min</th>
<th>24 Hrs</th>
<th>24½ Hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coag No</td>
<td>u1241</td>
<td>u1242</td>
<td>u1243</td>
<td>u1244</td>
<td>u1245</td>
<td>u1246</td>
<td>u1247</td>
<td>u1248</td>
</tr>
<tr>
<td>Factor VIII C</td>
<td>8.3</td>
<td>0.37</td>
<td>0.35</td>
<td>0.32</td>
<td>0.39</td>
<td>0.28</td>
<td>0.10</td>
<td>0.12</td>
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<tr>
<td>Factor VIII Cag</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor VIII Reg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti Ha (litre)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 ml plasma stored at -30°C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Notes:**

1. Dose should be infused in 20 minutes.
2. 10 ml plasma should be aliquoted (1 ml) and stored for future studies.
3. Patients selected for this study must be haemostatically stable.
4. Please return completed form to Dr F. Boulton, Edinburgh & South East Blood Transfusion Service, Royal Infirmary, Edinburgh.
PARTICULARS OF INFUSION:
Batch No. 60270
No. of Vials: 10
Volume infused: 19.8 mls.
Total dose: 198.0
If local VIII C assay on infusate was performed please give value and also
value & source of standard.
Solubility time: 30 minutes.
Infusion time: 17 minutes

<table>
<thead>
<tr>
<th>TIME</th>
<th>30 Before</th>
<th>1 hour</th>
<th>2 hours</th>
<th>3 hours</th>
<th>4 hours</th>
<th>5 hours</th>
<th>6 hours</th>
<th>24 hours</th>
<th>48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMPERATURE</td>
<td>36.5</td>
<td>36.7</td>
<td>36.3</td>
<td>36.25</td>
<td>36.5</td>
<td>36.9</td>
<td>36.5</td>
<td>36.4</td>
<td>36.4</td>
</tr>
<tr>
<td>BLOOD PRESSURE</td>
<td>100/50</td>
<td>120/70</td>
<td>130/75</td>
<td>130/75</td>
<td>130/80</td>
<td>125/80</td>
<td>120/80</td>
<td>120/80</td>
<td>120/80</td>
</tr>
<tr>
<td>PULSE</td>
<td>60</td>
<td>64.</td>
<td>76</td>
<td>76</td>
<td>80</td>
<td>85</td>
<td>84</td>
<td>84</td>
<td>84</td>
</tr>
</tbody>
</table>

Factor VIII C
Factor VIII Cag
Factor VIII Reg
Other Tests:

Number of 1mL aliquot stored at -20°C

NOTES:
1. Dose should be infused in 20 minutes.
2. Some plasma should be aliquoted (1 ml) and stored for future studies.
3. Patients selected for this study should be haemostatically stable.
(4) Please return completed form to Dr F Boulton,
Edinburgh & South East Blood Transfusion Service,
Royal Infirmary, Edinburgh.

Clinical Comments: Long run to disco no.
No side effects.
SNBTS HEAT TREATED FACTOR VIII IN VIVO RECOVERY AND LIFE STUDIES HAEMOPHILIA

PATIENT’S NAME: ........................................
HOSPITAL: ........................................ D.O.B. 6/02/61
BODY WEIGHT: 59.5 Kg. HEIGHT: 178 cms
CONSULTANT: DR. ........................................

PARTICULARS OF INFUSION:
Batch No. C312 69/370
No. of Vials: 40 Volume infused: 19.5 mls. Total dose: 1950 units
If local VIII C assay on infusate was performed please give value and also value & source of standard.
Solubility time: 55 minutes Infusion time: 20 minutes

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>11%</th>
<th>17%</th>
<th>23%</th>
<th>29%</th>
<th>35%</th>
<th>41%</th>
<th>47%</th>
<th>53%</th>
<th>69%</th>
<th>24%</th>
<th>24%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMPERATURE</td>
<td>36.4°</td>
<td>36.9°</td>
<td>36.9°</td>
<td>36.9°</td>
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<td>36.9°</td>
<td>36.9°</td>
<td>36.9°</td>
<td>36.9°</td>
<td>36.8°</td>
<td>36.8°</td>
</tr>
<tr>
<td>BLOOD PRESSURE</td>
<td>130/80</td>
<td>130/80</td>
<td>130/80</td>
<td>130/80</td>
<td>130/80</td>
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<tr>
<td>PULSE</td>
<td>80</td>
<td>100</td>
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<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

Factor VIII C □    □    □    □    □    □    □    □    □    □    □    □
Factor VIII Cag □    □    □    □    □    □    □    □    □    □    □    □
Factor VIII Rag □    □    □    □    □    □    □    □    □    □    □    □
Other Tests □    □    □    □    □    □    □    □    □    □    □    □
Number of ml aliquoted □    □    □    □    □    □    □    □    □    □    □    □
stored at -30°C

NOTES:
(1) Dose should be infused in 20 minutes.
(2) Some plasma should be aliquoted (1 ml) and stored for future studies.
(3) Patients selected for this study should be haemostatically stable.
(4) PLEASE RETURN COMPLETED FORM TO DR F BOULTON,
    EDINBURGH & SOUTH EAST BLOOD TRANSFUSION SERVICE,
    ROYAL INFIRMARY, EDINBURGH.

Clinical Comments

Clinical Comments

SNF 001 3003
**SNBTS HEAT TREATED FACTOR VIII IN VIVO RECOVERY AND LIFE STUDIES HAEMOPHILIA**

**PATIENT'S NAME:** [Redacted]  
**HOSPITAL:** [Redacted]  
**D.O.B.:** 6/10  
**BODY WEIGHT:** [Redacted] Kg  
**HEIGHT:** [Redacted] cms  
**CONSULTANT:** [Redacted]  

**PARTICULARS OF INFUSION:**  
**Batch No.:** C/312 - C/270  
**No. of Vials:** [Redacted]  
**Volume infused:** 19.8 ml  
**Total dose:** 19.8 ml  

If local VIII C assay on infusedate was performed please give value and also value & source of standard.

**Solubility time:** 5-5 minutes  
**Infusion time:** 20 minutes

<table>
<thead>
<tr>
<th>Time (Minutes)</th>
<th>Before</th>
<th>11</th>
<th>31</th>
<th>115</th>
<th>145</th>
<th>149</th>
<th>244</th>
<th>430</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEMPERATURE</strong></td>
<td>36.6</td>
<td>36.7</td>
<td>36.8</td>
<td>36.0</td>
<td>36.0</td>
<td>36.0</td>
<td>36.0</td>
<td>36.0</td>
</tr>
<tr>
<td><strong>BLOOD PRESSURE</strong></td>
<td>130/78</td>
<td>130/88</td>
<td>130/66</td>
<td>130/66</td>
<td>130/66</td>
<td>130/66</td>
<td>130/66</td>
<td>130/66</td>
</tr>
<tr>
<td><strong>PULSE</strong></td>
<td>80</td>
<td>100</td>
<td>84</td>
<td>94</td>
<td>94</td>
<td>94</td>
<td>94</td>
<td>94</td>
</tr>
</tbody>
</table>

| **Factor VIII C** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Factor VIII Cag** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Factor VIII Rag** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Number of I ml aliquots stored at -30°C** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

**NOTES:**  
1. Dose should be infused in 20 minutes.  
2. Some plasma should be aliquoted (1 ml) and stored for future studies.  
3. Patients selected for this study should be haemostatically stable.  
4. Please return completed form to Dr F Boulton, EDINBURGH & SOUTH EAST BLOOD TRANSFUSION SERVICE, ROYAL INFIRMARY, EDINBURGH.

**Clinical Comments:** Long long time to observe 4 hours interval until next injection

SNF:001:3004
**SNETS WHAT TREATED FACTOR VIII IN VIVO RECOVERY AND LIFE STUDIES HAEMOPHILIA**

**Patient's Name:**
**Hospital:**
**D.O.B.:**
**Body Weight:**
**Height:**
**Consultant:**

**Particulars of Infusion:**
- Batch No.: 0319 - 60270
- No. of Vials: 1
- Volume infused: 19.9 mls
- Total dose: 19.9 mls

If local VIII C assay on infusate was performed please give value and site:

**Solubility time:**
- Minutes

**Infusion time:**
- Hours

<table>
<thead>
<tr>
<th>Dose</th>
<th>Pre</th>
<th>20 Min</th>
<th>60 Min</th>
<th>120 Min</th>
<th>4 Hours</th>
<th>6 Hours</th>
<th>24 Hours</th>
<th>24+ Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temperature</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure</td>
<td>Coag No</td>
<td>01280</td>
<td>01281</td>
<td>01282</td>
<td>01283</td>
<td>01284</td>
<td>01285</td>
<td>01286</td>
</tr>
</tbody>
</table>

**Factor VIII C**
- Normal: 87
- 0.02
- 0.55
- 0.53
- 0.50
- 0.39
- 0.34
- 0.16
- 0.15

**Factor VIII Cagg**
- 0.53
- 0.51
- 0.49
- 0.37
- 0.37
- 0.14
- 0.13

**Factor VIII Reg**

**Anti-HE (litre)**

**10 ml plasma stored at -70°2**

**Notes:**
1. Dose should be infused in 20 minutes.
2. 10 ml plasma should be aliquoted (1 ml) and stored for future studies.
3. Patients selected for this study should be haemostatically stable.
4. Please return completed form to Dr F. Boulton,
   Edinburgh & South East Blood Transfusion Service,
   Royal Infirmary, Edinburgh.

Clinical Comments:
280 Trial Infusion

\[ \frac{50 \text{ ml/kg}}{1.5 \text{ ml/min}} \times 1050 \text{ ml} = 1575 \text{ ml} \]

\[ 1575 \text{ ml} - 1050 \text{ ml} = 525 \text{ ml} \]

\[ 525 \text{ ml} / 1.5 \text{ ml/min} = 350 \text{ min} \]

\[ \text{ Hematocrit} = 30\% \]

\[ \text{ Venous} = 77\% \]

\[ 13\frac{1}{2} \text{ hrs} \]
28 INFUSIONS

VOLUNTEER NO. 3

WEIGHT = 59.4 kg x 41 ml/kg = 2435 ml 

Plasma Volume

Recovery (Labelled Dosage) = 0.04 x 2435 = 66%

Recovery (Assauld Dosage) = 0.05 x 2435 = 76%

T1/2 = 12 hours

SUSAN HONE
**SNBTS HEAT TREATED FACTOR VIII IN VIVO RECOVERY AND LIFE STUDIES HAEMOPHILIA**

**PATIENT'S NAME:** [Redacted]

**HOSPITAL:** [Redacted]

**D.O.B.:** [Redacted]

**BODY WEIGHT:** 52 kg

**HEIGHT:** 173 cms

**CONSULTANT:** Dr. [Redacted]

**PARTICULARS OF INFUSION:**

- **Batch No.:** O3.2.86270
- **No. of Vials:** 10
- **Volume infused:** [Redacted] ml
- **Total dose:** [Redacted] ml

If local VIII C assay on infusate was performed please give value and also value & source of standard.

- **Solubility time:** 26-47 minutes
- **Infusion time:** [Redacted] minutes

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>15 min</th>
<th>30 min</th>
<th>1 hr</th>
<th>3 hr</th>
<th>6 hr</th>
<th>12 hr</th>
<th>24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEMPERATURE</strong></td>
<td>36.4°</td>
<td>36.7°</td>
<td>37.2°</td>
<td>37.5°</td>
<td>37.4°</td>
<td>37.2°</td>
<td>37.5°</td>
<td>37.2°</td>
</tr>
<tr>
<td><strong>BLOOD PRESSURE</strong></td>
<td>115/70</td>
<td>115/75</td>
<td>110/60</td>
<td>120/75</td>
<td>120/75</td>
<td>120/75</td>
<td>110/60</td>
<td>110/60</td>
</tr>
<tr>
<td><strong>PULSE</strong></td>
<td>88</td>
<td>82</td>
<td>60</td>
<td>60</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

**Factor VIII C**

- Before
- 15 min
- 30 min
- 1 hr
- 3 hr
- 6 hr
- 12 hr
- 24 hr

**Factor VIII Cag**

- ✓
- ✓
- ✓
- ✓
- ✓
- ✓
- ✓

**Factor VIII Rag**

- ✓
- ✓
- ✓
- ✓
- ✓
- ✓
- ✓

**Other Tests**

- [Redacted]
- [Redacted]
- [Redacted]

**Number of ml aliquot stored at -30°C**

- ✓

**Notes:**

1. Dose should be infused in 20 minutes.
2. Some plasma should be aliquoted (1 ml) and stored for future studies.
3. Patients selected for this study should be haemostatically stable.
4. PLEASE RETURN COMPLETED FORM TO DR. F. BOULTON,
   EDINBURGH & SOUTH EAST BLOOD TRANSFUSION SERVICE,
   ROYAL INFIRMARY, EDINBURGH.

**Clinical Comments:** No side effects.
**Patient's Name**: [Redacted]

**Hospital**: D.O.B.

**Body Weight**: 15.3 Kg

**Height**: [Redacted] cms

**Consultant**: [Redacted]

---

**Particulars of Infusion**: Batch No.

No. of Vials: [Redacted] Volume infused: 199 mls Total dose: [Redacted]

If local VIII C assay on infusate was performed please give value and also solubility time: [Redacted] minutes Infusion time: [Redacted] minutes

---

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Blood Pressure</th>
<th>Coag No.</th>
<th>Dose Pre</th>
<th>20 mins</th>
<th>60 mins</th>
<th>120 mins</th>
<th>4 hrs</th>
<th>6 hrs</th>
<th>24 hrs</th>
<th>24 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>W1376</td>
<td>W1377</td>
<td>W1378</td>
<td>W1379</td>
<td>W1380</td>
<td>W1381</td>
<td>W1382</td>
<td>W1383</td>
<td>W1384</td>
</tr>
</tbody>
</table>

**Factor VIII C**: 9.7 [Redacted] 0.73 0.61 0.43 0.43 0.39 0.13 0.12

**Factor VIII Cag**: 0.72 0.60 0.42 0.42 0.28 0.12 0.11

**Factor VIII Ag**: [Redacted]

**Anti HE (litre)**: [Redacted]

**10 ml plasma stored at -70°C**

**T_2 = 9 hours**

**Recovery (corrected dosage) =**

\[
\frac{0.92 \times 2.173}{199} = 81\% \\
\frac{16.08}{1950} = 0.2\%
\]

**Clinical Comments**: [Redacted]

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**Notes**: (1) Dose should be infused in 20 minutes.

(2) 10 ml plasma should be aliquoted (1 ml) and stored for future studies.

(3) Patients selected for this study should be haemostatically stable.

(4) Please return completed form to Dr F. Boulton, Edinburgh & South East Blood Transfusion Service, Royal Infirmary, Edinburgh.
### SUMMARY OF DATA FROM CLINICAL EVALUATIONS OF PEC FVIII PRODUCTS

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>DATE OF ASSESSMENT</th>
<th>NUMBER OF PATIENTS</th>
<th>LABELLED DOSAGE</th>
<th>ASSAYED DOSAGE</th>
<th>FIRST PHASE</th>
<th>SECOND PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNHEATED NY</td>
<td>Dec 1984</td>
<td>5</td>
<td>152 ± 8.1 %</td>
<td>-</td>
<td>2.83 ± 0.06</td>
<td>9.91 ± 1.38</td>
</tr>
<tr>
<td>NY : 2 hr/68 °C</td>
<td>MAY 1985</td>
<td>4</td>
<td>86 %</td>
<td>-</td>
<td>N.R</td>
<td>9.27 ± 2.36</td>
</tr>
<tr>
<td>NY : 24 hr/68 °C</td>
<td>MAY 1985</td>
<td>4</td>
<td>No Data</td>
<td>77.5 ± 9.3 %</td>
<td>N.R</td>
<td>11.63 ± 2.87</td>
</tr>
</tbody>
</table>

**NOTE:** N.R. = Not Relevant as no clearly defined first and second phases.