EXHIBIT "WITN3094001/29"

This is the exhibit marked "WITN3094001/1" referred to in the witness statement of Debra Anne Pollard dated 7 May 2019

(15)

Royal Free Hampstead NHS

NHS Trust

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28 January 2004

Dear Patient,

Re: RECOMBINANT ROLL OUT

The DoH have provided resource for a phased roll out of recombinant clotting factor. This will be on the basis of age (those up to the age of 40 years starting first) with everyone starting by April 2006.

At the Royal Free, we plan to provide this as patients attend the Centre to renew their home take out. We will need to obtain signed, informed patient consent and we appreciate there may be patients who prefer to stay on plasma derived product.

At the time of collection of new product we would plan to give guidance on the reconstitution and dosing of the recombinant product.

We will also need to check an inhibitor screen and pre and post FVIII or FIX level. A repeat inhibitor screen will be checked at the next 6 months review.

What do you need to do?

1. You should read the enclosed information in preparation to sign consent.
2. You should contact the front desk when you have only a few vials of plasma derived concentrate left to inform us when you propose to collect your home takeout.
3. You should bring all remaining vials of plasma derived concentrate to return to the Centre.
4. Ideally, if you use prophylaxis you should avoid treatment for at least 48 hours before attending the Centre.

Yours sincerely

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INFORMATION ABOUT RECOMBINANT CLOTTING FACTOR CONCENTRATE

INTRODUCTION

The Government announced in February 2003 that recombinant factor VIII and factor IX treatment would be made available to all people with haemophilia who wish to use them over the next three years. This information sheet seeks to provide you with information about recombinant clotting factors and particularly to assist those who are considering changing from plasma derived to recombinant treatment.

This change in clotting factor concentrate has been offered as a result of national guidelines (see below) and perceived safety issues relating to plasma derived concentrates. Current plasma-derived concentrates are manufactured with at least a single process to remove viruses, which is mainly effective against lipid-enveloped viruses for example HIV and hepatitis C; but it should be remembered that currently available and licensed plasma concentrates may still transmit non-lipid coated pathogenic viruses, for example Parvovirus B19. The safety of plasma-derived coagulation factor concentrates, therefore, depends, not just on steps to inactivate viruses during manufacturing, but also on other aspects like donor selection, number of donors to the plasma pool as well as the manufacturing procedure. The safest possible concentrates should be provided for future clinical use. Also, there has been some concern about the possibility of transmitting new infectious agents, for example vCJD.

In the UK there has been a move towards increasing numbers of patients (in particular all children from 1998) receiving recombinant concentrates. The first generation of these were manufactured using animal and human proteins in the cell culture medium and albumin, as a stabilizer, in the final vial. These are being

replaced by the second-generation concentrates in which the albumin in the final vial is replaced by non-protein stabilizers, and third-generation concentrates that lack added animal and human proteins in the cell culture medium and final vial. These are significant changes in the manufacturing process and will reduce the risk of recombinant concentrates transmitting infectious agents of animal or human origin.

GUIDELINES

Guidelines by the United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO) on the selection and use of therapeutic products to treat haemophilia were published in 2003 in the medical journal *Haemophilia* (volume 9, pages 1- 23). The specific recommendations for haemophilia A and B are:

"Haemophilia A - Recombinant FVIII is the treatment of choice. If recombinant FVIII is not available, a plasma-derived concentrate should be used".

"Haemophilia B - Recombinant factor IX is the treatment of choice. The only available product is currently not licensed for use in previously untreated patients or in those less that 6 years of age because of lack of clinical data and concerns about the risk of anaphylaxis. For these patients, however, on balance it is also recommended because no exogenous human or animal proteins are used in its manufacture. It must be infused with appropriate care and safeguards because of the risk of anaphylaxis. Anaphylaxis is a rare complication seen with the use of both plasma derived and recombinant FIX concentrates. The alternative to recombinant FIX is a high-purity plasma-derived FIX concentrate."

More detailed background information on which the recommendations are based are given below;

Recombinant concentrates

"In order to manufacture recombinant coagulation factors, the gene (or a modified gene) needs to be inserted into a cell line. The cells are cultured in a liquid culture medium and the secreted clotting factor is purified from this culture medium. The factor must be stable throughout the production process and when stored in the vial. Concern has been expressed over the use of human and animal products in the culture medium, and over the use of human albumin (a plasma derived product) as a stabilizer. If mouse monoclonal antibodies are used in the purification process, trace amounts may appear in the final product. There is the possibility of viral infection of the cell lines used to produce the clotting factor and any monoclonal antibodies used. For example contamination has resulted in the orbivirus bluetongue virus, which infects primarily sheep, infecting cell culture lines including those from Chinese Hamster Ovary (CHO), and CHO cells have also been contaminated by minute virus of mice. In addition CHO cells can also produce endogenous virus: (retroviral) particles, which suggests that even if all animal and human proteins can be removed from the production process a manufacturing step to remove viruses will enhance safety. A further consideration is that if a new mutation occurred in the clotting factor gene during cell culture a defective clotting factor could be produced and, if more immunogenic than the wild type clotting factor, may result in a higher incidence of inhibitors."

Summary of recombinant products available

	Cell line	Gene	Protein in culture medium	Murine mAbs	Human albumin as stabilizer	Viral inactivation Removal	Generation
Recombinate	CHO	VIII VWF	Bovine albumin, insulin, aprotinin	Yes.	Yes	No	1
Helixate Kogénate Bayer.	BHK	VIII	Human albumin	Yes	No	SD	2
Refacto	CHO	B-domain deleted VIII	Human albumin	Yes	No	SD	2
NovoSeven	BHK	VII	Bovine serum	Yes	No	SD	2
Benefix	CHO	IX	No	No	No	NF	3

BHK, baby hamster kidney; CHO, Chinese hamster ovary. SD, solvent detergent; NF, nanofiltration; mAbs, monoclonal antibodies.

- *First-generation recombinant coagulation factor concentrates*

"First-generation products have human albumin added to the final formulation as a stabilizer. Two first-generation preparations of recombinant FVIII were licensed in the early 1990s, Kogenate (Bayer) [also labelled as Helixate (Aventis-Behring)], which is no longer manufactured, and Recombinate (Baxter)."

- *Second-generation recombinant coagulation factor concentrates*

"Two newer recombinant FVIII preparations stabilized without the addition of human albumin are referred to as second-generation products, Kogenate Bayer (Bayer) [also labelled as Helixate Nexgen (Aventis Behring)] and ReFacto (Wyeth); both have human albumin in the cell culture medium."

- *Third-generation recombinant coagulation factor concentrates*

"In third-generation products, animal products have been removed from the culture media. Two recombinant FVIII products, Advate (Baxter) and ReFacto AF (Wyeth), manufactured and formulated without human or animal protein are under clinical trial; the latter does not use monoclonal antibodies in its preparation. The only recombinant FIX, Benefix (Baxter), has no human or animal protein used in its preparation or formulation."

At the present time we will be providing either Helixate (Aventis) for haemophilia A or Benefix (Baxter) for haemophilia B.

INHIBITORS to Factor VIII or Factor IX

There is no evidence to suggest that changing from plasma derived to recombinant concentrate will increase the risk of an inhibitor developing. There is a small but continuing risk of inhibitor development throughout life. This is why blood tests to

detect inhibitor development are performed when you attend review appointments. The current view is that recombinant products trigger no more inhibitors than plasma derived concentrates.

DEFINITIONS

Cell line – a cell that can be grown for many generations in culture medium. These have often been produced from cells originating in animals, for example hamsters.

Culture medium – liquid that contains substances and nutrients needed to keep cells alive and growing.

Gene – contains genetic code (blueprint) used by cell to make proteins, for example Factor VIII or Factor IX.

Mutation - change to the genetic code contained in a gene that results in failure to make the protein or making a faulty protein.

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