Guy's and St Thomas' Hospital NHS
NHS Trust

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CLINICAL DIRECTOR
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14th November, 2002.

Mr. David Kemsley,
Deputy Director of Commissioning,
Hillingdon Primary Care Trust,
Kirk House,
97-100 High Street,
Yiewsley, West Drayton,
MIDDX, UB7 7HJ.

Dear Mr. Kemsley,

Re: Provision of Recombinant Factor VIII for Adults.

I am writing to you to express my concern over the possible impact that new data on Recombinant Factor VIII of the brand Refacto, produced by Wyeth, may have upon clinical practice and possible expenditure on Haemophilia care across England.

I enclose, for your attention, the summary fact information/summary of product characteristics for Refacto, that are the product inserts with each vial. You will see that the summary is both in German, for treaters on the German market, and in English for English treaters. I am led to believe that the version of the product characteristics in French is identical with that of the German, and that a new version in English is soon to appear.

I bring to your attention item 4.4 in both enclosed documents headed in the German version as "Warnhinweise und VorsichtmaB-nahmen für die Anwendung" and as " Special Warnings and Special Precautions in Use" in the English version. To assist your assessment of the German document I enclose my translation.

It is abundantly clear that there are substantial differences in item 4.4, between the German and English product inserts. These relate to two fundamental issues:-

1. The German document implies, in the final three sentences of paragraph 2 under item 4.4, that after the market launch of ReFacto, a significant element of immunogenicity was observed with the appearance of high and low titre inhibitors in previously treated patients. This would seem to be greater than 0.8%, previously described in clinical trials.
2. The Germany document declares, in the third paragraph, under item 4.4 that following market launch and after clinical trials, a lack of efficacy became apparent in patients on continuous prophylaxis.

Information on these two issues do not appear in the English language product insert. This lack of information in the English document is remarkable, in that according to the EMEA, changes in the product insert should be done simultaneously across Europe for centralised licensed products, and a particular release date for individual countries should be posted. It is only in situations in which the changes are important, that implementation of changes in the product insert by individual countries may proceed ahead of an agreed release date.

I find these differences worrying in that their clinical and financial implications may be considerable. For the sake of brevity I will list my concerns:-

1. As ReFacto probably makes up some 30-40% of the current U.K. Recombinant Factor VIII market, any suggestion of immunogenicity or loss of efficacy could lead to

intervention by the Regulatory Authorities (MCA) to remove the product, either voluntarily or compulsorily, from the market. This could lead to a repetition of the difficulties experienced during 2001 and, inevitably, an increase in the price of other Recombinant Factor VIII products. As I am sure the MCA must be aware of all this information, reassurance should be sought from that agency.

2. The described problems associated with ReFacto are not shared (apparently) with other Recombinant Factor VIII products, and I can envisage an extremely difficult tendering process ahead for PASA in any attempt they may try to secure an all Recombinant purchase programme.
3. On the assumption that ReFacto demonstrates increased immunogenicity in previously treated patients, I can envisage the potential expenditure on Recombinant Factor VIIa and/or FEIBA increasing substantially in the management of patients who may have been relatively cheap to treat on previous therapy.
4. On the assumption that ReFacto demonstrates reduced efficacy in (some) patients on continuous prophylaxis, the additional cost for extra unitage to cover for this loss of efficacy must be anticipated and, accordingly, financial considerations must be adjusted upwards.
5. From my knowledge of the commercial market, the publication of this data on ReFacto suggesting these possible drawbacks (however large or small), will be seized upon by other Recombinant Factor VIII companies. In particular, Baxter may expedite their introduction of Third Generation Recombinant Factor VIII (at prices 55-60p/unit, exclusive of VAT) following their U.S. licence, which is anticipated to be awarded in April 2003. Naturally, a company as commercially astute as Baxter will, in all likelihood, withdraw the cheaper First Generation Recombinant Factor VIII product sooner rather than later with its associated cost implications.
6. At the National Haemophilia Foundation meeting held last week in Florida, it is reported that there will be a label change of the ReFacto product suggesting that Wyeth may be attempting to address the lack of efficacy issue by changing the analytical method, and possibly the standards used for measuring Factor VIII. It would seem unlikely that any such procedure may not necessarily make a profound difference in resolving the underlying clinical problems.

As I explained to you on the telephone, it could well be that I have over-reacted to what I perceive could be potential clinical and financial problems. From my prior knowledge of the market over many years I feel I must address these concerns, as all too often one's fears have been justified. I would be most obliged if you consider this document, and its enclosures, in light of the impending decision to fund Recombinant Factor VIII for all adults in England, and also from the Consortium's interest in securing a blood product contract through PASA.

I rely upon you to use the document, as you consider most appropriate.

Yours sincerely,

GRO-C

Professor G.F. Savidge, M.D.
Director, Haemophilia Reference Centre
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