Projected fees.

# CURRENT REGISTRATIONS U.K. AND EIRE

| | | Date of Submission | |
|---|---|---|---|
| **U.K.** | | | |
| **Endobulin** | | | |
| | Kawasaki | 22nd May 1990 | refund due |
| **FEIBA** | | | |
| | Change to Vapour | 3rd July 1990 | £2125/300 (1) |
| | Leaflet changes | 4th July 1990 | £300 |
| | Renewal due 17th October | | |
| **Gammabulin** | | | |
| | HPLC for fragments/aggregates | 15th March 1990 | 300 —(2) |
| | Removal Thiomersal | 24th April 1990 | 300 |
| **HAS 20%** | | | |
| | Ultra/dia filtration to replace lyophilisation | 27th July 1989 | ? (3) |
| **HAS 4.5%** | | | |
| | Ultra/dia filtration to replace lyophilisation | 27th July 1989 | |
| **Kryobulin** | | | |
| | Abridged application | 24th May 1990. | £5100 (5) |
| **Partobulin** | | | |
| | HPLC for fragments/aggregates | 15th March 1990 | £150 —(2) |
| | Removal of Thiomersal | ~~July~~ 29 June 1990 | £300 |
| **Prothromplex** | | | |
| | Change to Vapour | | (4) |
| **EIRE** | | | |
| **Endobulin** | | | |
| | Vienna response awaited | | |
| **Gammabulin** | | | |
| | HPLC for fragments/aggregates Plus removal of Thiomersal | 1st May 1990 | |
| **Kryobulin** | | | |
| | Renewal due 27th September | | |
| **HAS 4.5%** | | | |
| | New sizes 500 and 1,000 ml | 4th June 1990 | |

hcll

Vienna 31st May - 1st June 1990.

FEIBA

1. Completed MLA forms and revised pack insert supplied. Variations can now be submitted.

2. We need to consider the possibility of a further Variation to introduce the Hospital pack. Belfast are particularly keen on this - it is debatable how many U.K. users actually need the H.T. equipment. A change would also reduce storage space needed.

Registration

1. Tisseel

A Tisseel submission cannot be expected during 1990. The product is being totally reformulated to include Human Thrombin and also vapour heating plus a detergent inactivating step to reach something approaching 15 logs HIV inactivation. In addition I believe it is intended to produce the various 'ingredients' of Tisseel separately (fibrinogen, F XIII, fibronectin, Plasminogen) and then recombine them in a final formulation. This has the advantage of being able to introduce partitioning into the production process as well as viral inactivation to approach the necessary 15 logs.

An approximate date for completion of this work is early 1991. The question of clinical data remains open. Vienna are unwilling to resubmit before this time. Turn down of registration in the U.K. and also Norway has led to some problems with Austrian authorities. I think we need to consider our position in the U.K. and decide if we need to notify the MCA and possibly surgeons of our current position. Reasons for delay in resubmitting should be mainly the change to Human Thrombin.

In view of the potential absence of clinical work on the new product it was suggested a CTX or CTC might be our best approach. If we are to proceed down this line then additional staff at Head Office might be worth considering in view of the potential extra workload. The question of bovine Aprotinin still remains, however, and the best solution at this time would appear to be the purchase of final licensed product from Bayer (Trasylol). The current status of Trasylol in the U.K. with respect to BSE should be established and perhaps DPT could help here. Dr. Schwarz also suggested this should be discussed with PJC and also Dr. Burgess to determine who should approach Bayer.

2. C1 Esterase

Some data is available but not sufficient for U.K. authorities. Very little preclinical data is available and in subsequent discussions with Mrs. Frohlich she made a request for a U.K. clinician to carry out half life and in vivo recovery studies on the product. Draft proposals have been provided. If we are to approach any U.K. clinicians on this we need to consider the implications for Immuno sponsored work.

3. Gammabulin A

Currently there is insufficient raw material to even meet the demands of the German market. Problems exist with the Hepatitis A antibody test. Dr. Archer is currently working with Abbott to try and reach a solution.

The conversion of our Gammabulin licence to Gammabulin A is not, therefore, an immediate option.

4. Kryobulin

A new Kryobulin is in development which will have a specific activity of arrount 50 i.u./mg - produced by chromatography.

5. FSME

Whilst in principle Dr. Schwarz would leave to our judgement any decision on FSME registration he would point out potential risks. As the British Authorities are particularly critical they may find some problems which would have serious repercussions in Europe. Current sales are around $3.5 \times 10^6$ doses per year. The infection of the mice brains in particular might be the source of some problems. One solution might be to have the data reviewed by independent consultants prior to submission.

6. Igabulin

This would appear to be the best product for our next registration although preclinical data is rather sparse. Currently it is only licensed in Austria and the clinical data is based on only 1 study. Whether or not Gillian Roberts could produce a clinical section from 1 publication needs further discussion. Obtaining the actual background case data from Professor Eibl was also thought necessary but may not be achieved so easily.

7. CMV Immunoglobulin

An iv product based on Endobulin also seems attractive. A Canadian IND is in progress and the clinical side is rather sparse. The remainder, as the product is essentially CMV rich Endobulin, may not present a problem. Sufficient stock might be available for trials. A CTX would therefore be considered - a task for Mrs. Kunschak.

8. Endobulin Eire

The remaining open questions which were awaiting discussion between Dr. Jacobson and Dr. Schwarz were resolved fairly easily. We should expect a response in about 2 weeks.

9. Prothromplex

We should receive the Prothromplex data by the end of June.

10. Gillian Roberts

The work carried out for Kryobulin was not totally acceptable to Vienna but no real criticism of Gillian Roberts could realistically be made. She is not a haematologist and therefore some errors arose. This caused some problems for Mrs. Henninger and in addition Dr. Eibl did not like her English style which is more of an in house problem. Mrs. Diernhofer believes, however, that it will still be valuable to ask her to do work in the future. The Tisseel clinical project must, however, be shelved for the time being.

Mrs. Hettich

1. FSME

The orders for 500 and 300 should be supplied in June.

We need to notify our requests for booklets (with code reference) with each order. RWJ could do this.

In discussions with Dr. Krenn I raised the subject of short shelf life. This is a problem they are aware of as the antigen is relatively unstable. No immediate solution seems possible. We also discussed the question of English packaging. He was unaware of the potential problem this may cause and I have agreed to write to him on this and he will see if a solution can be found. The provision of English packing is, however, not so straightforward. Currently we are the only country who would take English packing although the Danes and Eastern Bloc countries might. To stop the packaging line to change to a different material takes approximately one day. To do this for 2-3,000 syringes is therefore uneconomical. As an alternative Dr. Krenn suggested an outer adhesive label with storage and administration details in English together with a statement to the effect that an English pack insert is enclosed. The printing of an English insert would be no problem. Another solution would be to wrap an English insert around the pack and secure with an elastic band. Both these options would be carried out in Vienna. Alternatively a larger quantity of English packing material stock could be produced with a good life and reserved for U.K., Denmark and Eastern Bloc.

The price of the vaccine will probably rise for 1991 since Sweden currently pay around AS110 and our price is lower - compounded by the recent fall in the pound. Sweden take c. 20,000/yr. Investigate possibility of inclusion in DHSS recommendations for travellers - impact on licensing decision.

Bulin stocks a little low for 1990 but if we need for 1991 for short term prophylaxis should be no problems. We should again consider obtaining more Bulin stocks for 1991 to cover short term prophylaxis.

2. Immunoplastin HTS

Mrs. Hettich needs some better idea of projected market share. They may be able to reduce the price by £1-£2 and give additional material foc. The need to maintain the status quo with other products vs Nycomed was emphasised. X

3. Human Normal Control Plasma

Their minimum price is 95p/ml calculated at 22 AS/£1. Therefore they are already below this figure. X

A 2 ml vial could be offered at 75p/ml (approx. - this needs to be confirmed) with a minimum order of 6,000 vials.

100 packs of 1 ml offer little additional saving.

4. Lupus Kit

Pricing of this will be discussed by Aschbauer/Rettich in second half of June.

5. Albumin

Mrs. Hettich would like early comment on production planning schedules - can anything be cancelled. Photocopies attached.

Endobulin

1. Pneumocystis

Details of titre to be provided to Igel and Dr. Hrabik. X

2. H.T. Manual

Mohr-Pennert believes could be of value and she will discuss with Koehler and Jacob. Dr. Hrabik can produce a draft. The approval of the scheme by Professor Eibl is seen as problematic. If we need home treatment packs in the U.K. we should go ahead and do these ourselves at this stage. Costs not resolved.

3. Liz Beek

RN to contact Liz to see what assistance needed. Wahn difficult to speak to. Auerswald in Bremen has 2 or 3 children on Endobulin home treatment.

4. IgAbulin

Brochure translation available for Webster. Next development could be enteric coated lyophilised IgAbulin for Crohns disease (confidential).

5. ADR

NIH summary of ADR with IVIG shows Endobulin best.

6. EGID Meeting

Investigate possibility of Dr. Hrabik attending. X

7. Kawasaki

No promotional brochure in Vienna.

8. Guillain Barre

Starting to be a good indication.

9. Dr. Hrabik would welcome opportunity to spend time in Kent to improve English.

Protein C.

Clinical trial in Germany progressing. Possibly another year of work then registration. As it is monoclonally purified check C PMP position.

Partobulin

Krenn reports Eder has found errors in training manual but wont be specific. RN to write to Eder (cc Krenn) to try and get m re details as Reps. need to be informed. X

Tisseel

1. Liposuction Video.

Should be available in 2-3 weeks. X

2. Tissomat

Best solution will be to obtain U.K. standard tubing and Biegler will modify. Details of size and manufacturer needed.

Albumin

Suggested Aluminium warning in conflict with EP labelling recommendations. Another text provided to be amended and sent to Mrs. Diernhofer for comment.

Mrs. Meissner - Meetings/FSME

1. Nato Meeting

Vienna wish to attend - book minimum stand £750 - Vienna to reimburse costs.

Macher will attend and bring exhibition stand.

He would welcome someone from U.K. during the week. This needs discussion in U.K. Two hotel rooms to be booked.

2. FSME

Current recommendations of 2 doses 2 weeks apart 1-2 weeks before travel are valid. Recent studies show seroconversion after 2 doses is in excess of the 95% quoted. However this should not be used outside the Company. It is confirmed that one dose is no good for protection.

Booklet still valid in terms of ADR risks. Recommendation for children is still over 1 year of age. Spacing of vaccinations may be advisable in the very young. A 3 month old baby has recently caught TBE. Kunz has recommended 0.3 ml doses for under 1 year. However, Government recommendation is still for only over 1 year. There is something of an unresolved conflict. New statistics on Austrian vaccination rates etc. provided. There is now a patient group established of TBE sufferers which publish awareness material.

3. ISHT

Details given to Mrs. Meissner - she feels £50,000 - £100,000 is too expensive - will discuss with Eibl - possibility of discussions in Barcelona mentioned.

Rogy - Drugs & Therapeutics Bulletin

Articles provided - Crescenzi translation to be inserted and sent to Rogy. Some unlicensed indications provided and NIH report to be included.

Schoppmann

1. Fibrinogen

Reconstitution should only take 10-15 minutes with 2% solution. 1% solution should be quicker - RN to check batch Nos. at St. Thomas'.

2. Feiba

U.S. brochure text provided with a request for comment prior to making a neutral English folder.

3. LMW - Heparin

For internal use only? Confidential. Vienna have Opocrin sublicence - CP have sublicence for U.K. There are problems with Opocrin - licence has been turned down due to lack of clinical data.

Vienna may approach Kabi for co-marketing rights - Kabi co-market is Switzerland.

GRO-C

RN/BSH
5.6.90