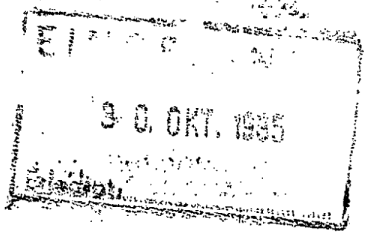
Immuno Ltd

Arctic House, Rye Lane, Dunton Green,
Nr Sevenoaks, Kent TN14 5HB

Telephone: Sevenoaks (0732) 458101
Telex: 95413



RN/JER

October 25th, 1985

Mrs. Diernhofer,
Immuno A.G.

Dear Mrs. Diernhofer:

Please find enclosed copies of the balance of the registration correspondence for Feiba as mentioned in my recent telex. In addition a copy of the actual Licence Document together with the requirements on reporting suspected adverse reaction are also enclosed.

As a new product to the U.K. market Feiba has, not unexpectedly, been subject to the special reporting requirements and our data sheets in the U.K. will be marked with a black triangle as is currently applied to Kryobulin heat treated.

Kind regards.

Yours sincerely,
for IMMUNO LTD.,

GRO-C

R. Nicholson, M.Sc.,
Marketing Manager.

Enc.

Department of Health and Social Security
Medicines Division
Market Towers 1 Nine Elms Lane London SW8 5NQ
Telex 883669 Telephone 01-720 2188 ext
GTN 2814

Immuno Limited
Arctic House
Rye Lane
Dunton Green
Nr Sevenoaks
Kent TN14 5HB

Your reference

Our reference PL 0215/0021-0022

Date 17 October 1985

Dear Sirs

MEDICINES ACT 1968: PART II LICENSING

I refer to your application dated 25 September 1981 as amended by your letters of 26 October 1982, 9 October 1982, 1 June 1983, 7 June 1983, 7 July 1983, 29 Oct. 1984, 20 December 1984, 28 August 1985, 1 October 1985 and letters dated 17 November 1983 from Monoject and 6 December 1983 from Transcodan.

Authority has now been given for the grant of a product licence for:

PRODUCT	LICENCE NUMBER
Feiba Immuno Factor VIII Inhibitor Bypassing Fraction Human Heat Treated	PL 0215/0021-0022

The formal documents are enclosed. If you consider they contain information which is incorrect or is not in accordance with your application and amendment(s) please return them with brief details.

In relation to the above licence you will wish to note and consider the following:

1. The licence is subject to standard provisions which are contained in the schedule to the licence.

2. Your attention is drawn to the requirements concerning the reporting of suspected adverse reactions under Article 4 of Schedule I (Part 1) to the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (SI 1971 No 972) Attached is a Standard Direction and Guidance Notes which set out these requirements.

3. Special reporting instructions apply to this product (see paragraph 3 and 4 of the Standard Directions). You should mark this product with a black triangle in the data sheet. You may apply to the Licensing Authority after four years for this to be removed.

4. If any data sheets for the product(s) covered by this/these licence(s) are to be issued will you please arrange for copies to be sent to this office. The particulars to be included in such sheets are set out in the Medicines (Data Sheet) Regulations 1972 (SI 1972 No 2076).

5. Please let me know the date(s) on which the product(s) is/are introduced on to the market. In the case of proprietary products the enclosed gazette letter should be completed and returned.

6. The Tear-off portion of the enclosed letter concerning disposal of spare data should be returned as soon as possible.

7. This product is subject to batch release procedure as stated in the appropriate letter attached.

Yours faithfully

GRO-C

MISS A SHOOB

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Department of Health and Social Security
Medicines Division
Market Towers 1 Nine Elms Lane London SW8 5NQ
Telex 883669 Telephone 01-720 2188 ext
GTN 2814

Immuno Limted
Arctic House
Rye Lane
Dunton Green
Nr Sevenoaks
Kent TN14 5HB

Your reference

Our reference 0215/0021-0022

Date 17 October 1985

Dear Sirs

MEDICINES ACT 1968: PART II LICENSING

In accordance with the provisions of Product Licence number 0215/0021-0022 the Licensing Authority hereby

1 REQUESTS that:

i. samples of four bottles of the finished product, together with full protocols of the tests which have been applied to each batch of Feiba Immuno Factor VIII Inhibitor By-passing Fraction Human Heat Treated be sent to Dr D Thomas
Division of Blood Products
National Institute for Biological Standards and Control, Holly Hill, Hampstead, London NW3 6RB;

ii. the samples submitted are collected so as to be truly representative of the relevant batch and, if this is not the case, the method of sampling stated;

iii. each dosage container submitted be labelled with the final labelling, unless there are stated valid reasons for not so doing, in which case a specimen of the final label is to be provided and every dosage container labelled with the name of the product, batch number, dosage and the name of the company;

2. DIRECTS that:

no such batch be sold or supplied or offered for sale or supply until a certificate authorising its sale or supply has been issued by or with the consent of the Licensing Authority.

Yours faithfully

GRO-C

MISS A SHOOB

TJ/15

MEDICINES ACT 1968

PRODUCT LICENCE NO. 0215/0021-0022 has been granted under and subject to the provisions of the Medicines Act 1968 to

Immuno Limited
Arctic House
Rye Lane
Dunton Green
Nr Sevenoaks
Kent TN14 5HB

in respect of the products, particulars of which are set out in Part 1 of the attached Schedule. The Licence is subject to the further provisions set out or referred to in Part 2 of the said Schedule.

This Licence, unless previously suspended, revoked or varied as to the period of its validity, shall continue in force until the end of a period of five years from the date on which it was granted.

Date granted: 17 October 1985

GRO-C

A person authorised to sign on behalf of the Secretary of State for Social Services.

17 October 1985

Department of Health and Social Security
Medicines Division
Market Towers
1 Nine Elms Lane
LONDON SW8 5NQ

MEDICINES ACT 1968

Product Licence No. 0215/0021-0022

SCHEDULE

Part 1 - PARTICULARS OF THE PRODUCTS TO WHICH THE LICENCE RELATES

1.	Name of Product:	FEIBA IMMUNO FACTOR VIII INHIBITOR BYPASSING FRACTION HUMAN HEAT TREATED
2.	Pharmaceutical form:	Lyophilised substance and solvent (Water for Injections B.P.) to form an intravenous injection.
3.	Active constituents:	The product is available in the following strengths, 500 or 1000 FEIBA units*. *One FEIBA unit is defined as the FEIB-activity which shortens the activated partial thromboplastin time of a high titre Factor VIII inhibitor reference plasma (IMMUNO house standard inhibitor plasma, lyophilised) to 50% of the blank value.
4.	Uses:	FEIBA IMMUNO is mainly used to control bleeding episodes in haemophilia A patients with Factor VIII inhibitors and in patients with acquired Factor VIII inhibitors.
5.	Recommended dose and dosage schedule:	A. Factor VIII-Inhibitor Patients On the basis of available clinical trial results obtained in the treatment of Factor VIII inhibitor patients it is possible that FEIBA's effectiveness may vary between patients, this may be due to varying inhibitor titres and other, as yet unknown, factors. As a result larger doses may be necessary if the inhibitor titres are high, but this is not a general rule. The determination of the Whole Blood Clotting Time (WBCT) according to Lee White and/or the calculation of the r-value in the thrombelastogram (TEG) help to determine the most effective dose and to check the success of therapy. Care must be taken to distinguish between the following indications. Spontaneous bleeding episodes A dosage of 50 to 100 units per kg bodyweight administered in 8-to 12-hourly intervals is recommended and should be continued until

MEDICINES ACT 1968

Product Licence No. 0215/0021-0022

SCHEDULE

Part 1 - PARTICULARS OF THE PRODUCTS TO WHICH THE LICENCE RELATES

5. Recommended dose and dosage schedule: (continued)

clear signs of therapeutic improvement appear. This means, in the case of exterior bleeding, healing of the bleeding site, or in the case of internal bleeding, a lessening of pain, reduction in swelling or mobilisation of the joint. If there are no signs of therapeutic improvement despite the administration of 100 units of FEIBA per kg given 8-hourly, combined therapy with 40 units per kg of a Factor VIII concentrate (KRYOBULIN or FACTOR VIII CONCENTRATE HUMAN IMMUNO) is recommended. The Factor VIII must be administered after each individual dose of FEIBA.

In home treatment of bleeding complications up to 150 U/kg bodyweight have been administered, the effective dose very likely depending on the extent of bleeding. In some cases a kind of maintenance prophylaxis was successfully undertaken in home treatment with three applications weekly of approximately 30 units of FEIBA IMMUNO per kg bodyweight followed by approximately 60 units of Factor VIII concentrate per kg.

Minor surgery

Basically, the same kind of therapy should be followed as in the case of spontaneous bleeding episodes. It is, however, necessary to check the substitution effect before the operation and, if necessary, increase the dose or give consideration to combined treatment with Factor VIII Concentrate (40 units per kg).

For checking effectiveness, the following tests should be carried out.

Whole Blood Clotting Time (WBCT) according to Lee White r-value of the thrombelastogram (TEG).

When combination therapy with Factor VIII concentrate is used the Activated Partial Thromboplastin Time (APTT) may be shortened to normal values.

MEDICINES ACT 1968

Product Licence No. 0215/0021-0022

SCHEDULE

Part 1 - PARTICULARS OF THE PRODUCTS TO WHICH THE LICENCE RELATES

5.	Recommended dose and dosage schedule: (continued)	Since disseminated intravascular coagulation (DIC) cannot be totally excluded in the course of this treatment. It is advisable to carry out repeated tests on platelets fibrinogen and FDP
6.	Contra-indications, Precautions and Warnings:	Contra-indications: Presence of disseminated intravascular coagulation (DIC). Precautions and warnings: Before each individual application of FEIBA IMMUNO with Factor VIII inhibitor patients it is advisable to count the patient's platelets, since some investigators have found that FEIBA's effectiveness depends on the presence of a normal number of platelets. If the number of platelets is below 100,000/mm^3 this should be normalised by giving platelet-concentrate before administering FEIBA IMMUNO. In this connection special attention must be drawn to the platelet drop which follows the use of animal AHG, which may render FEIBA IMMUNO ineffective.
7.	Legal Category:	PRESCRIPTION ONLY MEDICINE
8.	Method of retail sale or supply:	The product will be made available only through Haemophilia Treatment Centres.
9.	Manufacturer of dosage form:	ÖSTERREICHISCHES INSTITUT FÜR HAEMODERIVATE GES. M.B.H. Subsidiary of IMMUNO AG Industriestrasse 72 A-1220 Vienna Austria

MEDICINES ACT 1968

Product Licence No. 0215/0021-0022

SCHEDULE

Part 2 - FURTHER PROVISIONS SUBJECT TO WHICH THE LICENCE HAS BEEN GRANTED

1. All the provisions of Part I of Schedule 1 of the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (SI 1971 No 972) as amended by the Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1972 (SI 1972 No 1226), the Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1974 (SI 1974 No 1523). The Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1977 (SI 1977 No 675) and the Medicines (Standard Provisions for Licences and Certificates) Amendment (No 2) Regulations 1977 (SI 1977 No 1039) shall apply.

2. Leaflets issued with proprietary medicinal products shall comply with the requirements of the Medicines (Leaflets) Regulations 1977 (SI 1977 No 1055). Labels of medicinal products shall comply with the Medicines (Labelling) Regulations 1976 (SI 1976 No 1726) as amended by the Medicines (Labelling) Amendment Regulations 1977 (SI 1977 No 996).

3. The product(s) shall not be recommended to be used for any purposes other than those specified in Part 1 of this Schedule as Uses.

4. The specification of the constituent and of the finished product shall be in accordance with the information contained in the application for this product licence.

5. The product shall be manufactured only in accordance with the method given in the application for this product licence.

6. This product may be sold or supplied only in accordance with a prescription given by an appropriate practitioner.

Standard Direction

(Human Medicines)

MEDICINES ACT 1968

DIRECTION AS TO REPORTING OF SUSPECTED ADVERSE REACTIONS

Product Licence No ....0215/0021-0022.....

Granted to .....Immuno Limited.....

In respect of .....Feiba Immuno Factor VIII Inhibitor Bypassing Fraction Human Heat Treated

1. In pursuance of para 4 of Part I of Schedule 1 to the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (SI 1971 No 972) as applied to the licence described above, the licensing authority directs the holder of the licence to furnish to the authority, for the information of the Committee on Safety of Medicines, except where the holder of the licence has already furnished the Committee with the information and received an acknowledgement, copies of such reports originating in the United Kingdom or abroad, and of which he is aware, of adverse effects in human beings suspected of association with the use of the medicinal product to which the licence relates as indicated in the paragraphs 3 to 6 below. The holder of the licence is required to furnish such reports as soon as possible after receipt, or where appropriate, immediately after substantiation by the patient's doctor. Licence holders should ensure that in all cases such reports are furnished not later than one month after receipt.

2. This direction applies to reports which have been made by, or confirmed by a medical or dental practitioner, a coroner, or a procurator fiscal.

PRODUCTS CONTAINING NEW ACTIVE SUBSTANCES OR PRODUCTS WITH A NOVEL FORMULATION CONTAINING AN ESTABLISHED ACTIVE INGREDIENT

3. For a period of 4 years (or more at the discretion of the licensing authority) after the date of gazetting of the licence for a product containing a new active substance on the United Kingdom market or a product with a novel formulation containing an established active ingredient the holder of the licence is required to furnish to the licensing authority copies of all individual reports of adverse reactions associated with the use of the product in the United Kingdom. (See paragraph 6 below in respect of reports arising from clinical studies after marketing conducted in the United Kingdom).

4. Reports of adverse reactions associated with the use of such products abroad should be furnished to the licensing authority where the reaction was serious; and where such a reaction had not previously been referred to in the product's data sheet or in the standard scientific literature. For the purpose of this direction "serious reaction" means that the reaction is fatal, life-threatening, disabling or incapacitating.

ALL OTHER DRUGS

5. The holder of the licence is required to furnish to the licensing authority copies of any reports of individual adverse reactions associated with the use of the product which are serious; that is fatal, life-threatening, disabling or incapacitating, where these originate in the United Kingdom. Reports of such

reactions associated with the use of the product abroad are required only where these are not referred to in the product's data sheet or in the scientific literature. Reports of other less serious reactions are not required.

CLINICAL STUDIES AFTER MARKETING (ALL PRODUCTS)

6. Copies of reports of adverse reactions to the licence holders products which come to their attention during clinical studies after marketing conducted in the United Kingdom or abroad are required to be furnished to the licensing authority in summary form at the end of the study. Any such reaction which is serious; that is fatal, life-threatening, disabling or incapacitating; must however be reported to the licensing authority not later than one month after receipt.

GENERAL

7. This direction is without prejudice to any specific direction made in connection with a particular product and remains in force until withdrawn or amended by a fresh notification in writing by the licensing authority.

8. This direction supersedes all previous standard and special directions which are hereby cancelled.

MEDICINES DIVISION
DHSS

GUIDANCE ON ADVERSE REACTIONS REPORTING BY COMPANIES

1. The legal requirements on the reporting by companies of adverse reactions to their products are set out in a number of statutory instruments and in a standard direction. The major statutory instruments are:-

The Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 No 972.

The Medicines (Applications for Product Licences and Clinical Trial and Animal Test Certificates) Regulations 1971 No 973.

The Medicines (Exemption from Licences) (Clinical Trials) Order 1981 No 164.

2. The requirements imposed on companies by the statutory instruments and the direction together with additional guidance are given below and summarised in tables 1 and 2 (on page 4).

3. Reports of suspected reactions should contain the following basic information: the name (or an identifying code) of the patient; the reporting doctor's name and address; the name(s) of the drug(s) which the patient was taking; the details of the reaction . It is important that suspected reactions should be confirmed in writing to the company by the patient's own doctor or dentist. In some cases, as when a report has been made verbally to a company, it will be appropriate to seek such substantiation before reporting a reaction. Companies should not, however, wait for the outcome of the reaction before reporting and should not draw distinctions between "conceivable" and "suspect" reactions to justify failing to report some reactions. Companies need not send in reports of particular cases of reactions published in the standard scientific literature.

REPORTS OF REACTIONS ORIGINATING IN THE UK

4. Reports on products subsequent to marketing

i. New Products - All products containing new chemical entities (or novel formulations of existing substances) are the subject of special reporting arrangements. Companies will be told of the need to follow the special reporting arrangements when the product licence is granted. They should mark such products with a ▼ in the Data Sheet. The special reporting arrangements will usually last for a period of four years from the date the grant of the licence is published in the London Gazette. After that period companies may apply in writing to the Licensing Authority for the ▼ to be removed from the data sheet and the special reporting arrangements cease. Where there is any delay in marketing the product the four year period may be taken from the date of first marketing in the UK. In other cases the licensing authority may retain the special reporting system for longer than four years. All spontaneous reports from doctors whether serious or otherwise should be submitted to the licensing authority immediately. (See paragraph 3 above) As regards reactions arising from clinical studies after marketing companies should submit reports of serious reactions immediately; other minor reactions from such studies should be reported in a summary after they are concluded. (N.B For the purpose of this guidance "serious" means fatal, life-threatening, disabling or incapacitating. Examples of serious reactions are

anaphylaxis, blood dyscrasias, congenital abnormalities, endocrine disturbances, fertility effects, haemorrhage from any site, jaundice (however mild), ophthalmic disorders, severe CNS effects, severe skin reactions, reactions in pregnant women.)

ii. Other Drugs

Serious reactions whether arising spontaneously or from clinical studies after marketing should be reported immediately (including serious reactions associated with other products where these are included in such studies). Spontaneous reports of minor reactions need not be reported. Minor reactions occurring during clinical studies after marketing should be reported in summary form on the conclusion of the study.

5. Products Under Trial

i. Products subject to clinical trial certificates (CTC)

Companies are required to inform the Licensing authority of any information which casts doubts on the continued validity of the data submitted with the application for a CTC in relation to the safety of the product in its proposed indications. Serious reactions should be submitted immediately; all other reports should be provided in summary form at the conclusion of the trial. All investigators should be informed of serious, unpredictable reactions occurring in the trials. Companies are required to inform the licensing authority if a trial involving the use of the product is discontinued, giving the reasons it has been discontinued.

ii. Products subject to clinical trial exemption (CTX)

Companies are required to inform the licensing authority forthwith of any adverse reactions or effects associated with the administration of the medicinal product. Speed in reporting is particularly important with serious reactions. All investigators should be informed of serious, unpredictable reactions occurring in the trials.

REPORTS ORIGINATING ABROAD

6. Reports on all products subsequent to marketing - Reactions which are both serious and unpredictable ("unpredictable" means not previously referred to in the data sheet or the scientific literature) should be reported immediately. Reports of other reactions are not required. (It it obviously important that companies should ensure a prompt exchange of information on adverse reactions between the parent company and subsidiaries if this requirement is to be implemented effectively).

7. Products under trial

i. Products subject to CTC's

All serious and unpredictable reactions should be reported immediately. Other reactions should be submitted in summary form either at the conclusion of the UK trials or in any product licence application.

ii. Products subject to CTX

Companies are required to inform the licensing authority forthwith of

any adverse reaction, whether serious or not, associated with the administration of the product. Speed in reporting is particularly important with serious reactions.

PRODUCT LICENCE APPLICATIONS

8. Companies are asked to bear a number of specific points in mind when submitting product licence applications. They are required to submit with their applications, and in the period until their licence application has been determined by the licensing authority, summaries of all adverse reactions reported to them arising out of the clinical trials, whether or not these trials are undertaken in the UK. These reports should include not only patients involved in the trial on a formal basis but also reactions in patients treated with the product on the clinician's own responsibility outside the trial protocol. Moreover companies should report all clinical events which are reported to them as adverse reactions by the responsible clinician whether or not they believe them to be reactions caused by the product and whether or not the product was being used outside the terms specified in the trial protocol, at the time the reaction occurred. In addition, the licensing authority expects companies to submit with their applications summaries of serious and unpredictable reactions occurring in other countries where the product is already licensed including anecdotal reports or reports arising from clinical studies after marketing.

METHOD OF REPORTING

9. Individual reports and summaries of reports should be sent to:

Licensing Authority
Adverse Drug Reaction Section
Room 1427
Market Towers
1 Nine Elms Lane
London SW8 5NQ

Individual reports should be submitted on yellow forms. Companies may produce summaries in any form they feel appropriate.

Reactions Originating in the UK

TABLE 1

	Serious Reactions	Minor Reactions
a) Licensed Products		
Spontaneous reports (New Drugs)	A	A
Spontaneous reports (Other Drugs)	A	not required
Clinical studies after marketing (new drugs)	A	B
Clinical studies after marketing (other drugs)	A	B
b) Products under trial		
CTC	A	B
CTX	A	A

TABLE 2

Reactions Originating Abroad (including those in clinical studies after marketing)	Serious and unpredictable reactions	Minor or predictable reactions
Products licensed in the UK	A	not required
Products under CTC in the UK	A	C
Products under CTX in the UK	A	A

Notes

1. "serious reactions" means all fatal, life-threatening, disabling, or incapacitating reactions

2. A = report on yellow forms immediately

3. B = report in summary at conclusion of trial or study

4. "Unpredictable" means not previously referred to in the data sheet or the scientific literature

5. C = report in summary form at the conclusion of the UK trials or at the time of a product licence application

IN CONFIDENCE

CSM/AR/IND
B/M272/086

REPORT ON SUSPECTED TOXICITY OR SIDE-EFFECTS

For the information of THE COMMITTEE ON SAFETY OF MEDICINES

NOTES FOR GUIDANCE

1. For all drugs, please record serious or unusual reactions. For new drugs record all reactions.
2. Record, on the top line, the drug suspected of causing harmful effects to the patient at normal dosage.
3. Record all other drugs, including self-medication, taken in the previous 3 months. With congenital abnormalities, record all drugs taken during pregnancy.
4. Please do not be deterred from reporting because some details are not known.

Name of Patient: (Required in confidence to allow linkage with other reports for same patient)	From (Name and address): Company doctor or other representative of product licence holder— Signed: Date:
Sex / Age or Date of Birth / Weight if known	Name of patient's own doctor (and address if known):

DRUGS* (Brand name where appropriate)	ROUTE	DOSE	DATES From	DATES To	INDICATIONS
(*For Vaccines give Batch No.)					

REACTIONS (List separately)	Started	Ended	OUTCOME (e.g. fatal: recovered)

Additional Notes

IN CONFIDENCE

CSM/AR/IND
B/M272/086

REPORT ON SUSPECTED TOXICITY OR SIDE-EFFECTS

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(*For Vaccines give Batch No.)					

REACTIONS (List separately)	Started	Ended	OUTCOME (e.g. fatal: recovered)

Additional Notes

IN CONFIDENCE

CSM/AR/IND
B/M272/086

REPORT ON SUSPECTED TOXICITY OR SIDE-EFFECTS

For the information of THE COMMITTEE ON SAFETY OF MEDICINES

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DRUGS* (Brand name where appropriate)	ROUTE	DOSE	DATES From	DATES To	INDICATIONS
(*For Vaccines give Batch No.)					

REACTIONS (List separately)	Started	Ended	OUTCOME (e.g. fatal; recovered)

Additional Notes