COMMERCIAL - IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

appendix 'A'

12A

PL/0010/0061

Bayer UK Limited

ANTI-HAEMOPHILIC FACTOR (HUMAN) KOATE

(Blood Product)

Sub-Committee on Biologicals - January 1976.

Recommendation

On the evidence before them the Sub-Committee recommend the grant of a product licence for this preparation for the purposes indicated in the application on condition that:

1) Satisfactory information is provided on

   a) the number of donations in each pool;

   b) the method of assay, the standard used and its calibration;

   c) batch to batch reproducibility.

2) The product labelling complies with the BP, including the use of international units of potency, and showing the upper limit of the storage temperature as 6°C.

3) The expiry date is given together with temperature at which the investigation was performed.

4) On-going information is provided on the reasons for, and the rate of, rejection of donors or donations, centre by centre.

5) The applicant shall agree to the imposition of the batch release procedure, to be applied at the licensing authority's discretion.

Remark

The company should be asked to provide any available information on the antifactor-VIII antibody levels in patients treated with this material who have been suitably followed up.

Main Committee - January 1976.

Advice

On the evidence before them the Committee advise the grant of a product licence for this preparation for the purposes indicated in the application on condition that:

1) Satisfactory information is provided on

   a) the number of donations in each pool;

   b) the method of assay, the standard used and its calibration;

   c) batch to batch reproducibility.

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(Contd.)

2) The product labelling complies with the BP, including the use of international units of potency, and showing the upper limit of the storage temperature as 6°C.

3) The expiry date is given together with temperature at which the investigation was performed.

4) On-going information is provided on the reasons for, and the rate of, rejection of donors or donations, centre by centre.

5) The applicant shall agree to the imposition of the batch release procedure, to be applied at the licensing authority's discretion.

It was decided that if the applicant did not agree to these conditions, a letter should be sent by the Secretary in accordance with Section 21(1) of the Medicines Act.

The Committee also advise that this product should be indicated as "recently introduced" and should be the subject of a special directive for the reporting of adverse reactions.

NOT FOR PUBLICATION

CONFIDENTIAL - IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

Sub-Committee on Biological Substances

MEDICINES ACT 1968
APPLICATION FOR A PRODUCT LICENCE

Product Licence Number	PL/0010/0061 1A
Date Received	21-10.75
Meeting	January 1976
Medical Assessment by	Dr R D Andrews
Pharmaceutical Assessment by	Mrs M-R Pratt
Therapeutic Class	Blood Product

Summary, Report and Recommendation

1. PRODUCT SUMMARY

1.1 Name: Anti-haemophilic Factor (Human) Koate™

1.2 Pharmaceutical form and active constituent(s): A sterile lyophilised powder for reconstitution with sterile water for injection, for IV use. Vials contain 250 or 500 units of Factor VIII.

1.3 Licence to be held by: Bayer UK Limited
Richmond, Surrey

1.4 Period of validity: 5 years

1.5 Manufacturer: Cutter Laboratories Inc
Berkley
California 94710, USA

1.6 Applicant's proposed method of sale: By direct government contract and private sale.

1.7 Legal status:

1.8 Consideration by other committees: Date:

a. Sub-Committee on Toxicity and Clinical Trials: N/R

b. Sub-Committee on Chemistry, Pharmacy and Standards: N/R

2. PHARMACEUTICAL COMMENT

The specification for the bulk active substance (p.42 of the Chemistry and Pharmacy Volume) does not include any limits for the tests.

The stability data provided was for temperatures 5°C and 25°C; the company propose to recommend storage of the product at 2-8°C.

3. CLINICAL USE

3.1 Use

For the treatment of classical haemophilia in which there is a demonstrated deficiency of Factor VIII.

3.2 Recommended dose

This is dependent upon the individual needs of the patient and is based upon weight, severity of the deficiency and/or haemorrhage, the presence of inhibitors and the Factor VIII level desired.

3.3 Precaution and contra-indications

The company literature includes the usual warning about the presence of hepatitis B virus and recommends restricting its use to Factor VIII deficiency only. The product should be stored below 8°C until reconstituted when it must be used within 3 hours. (To avoid possible bacterial contamination).

4. MANUFACTURE

4.1 Manufacturer:- Cutter Laboratories Inc
Berkley
California 94710
USA

4.2 Method of Manufacture

4.2.1. Source Material

Each plasma donation is currently tested by radioimmuno assay (RIA) for hepatitis B antigen according to the mandatory FDA requirement as of 15.9.75. No reports have been received attributing hepatitis to Koate since its introduction in February 1974. The raw material is supplied by no less than 54 different firms which are classified in the submission according to whether the firm is owned and operated by others or Cutter owned, whether the plasma is collected by plasmapheresis or obtained from whole blood or whether the apparatus used is owned by Cutter or the firm concerned. The list includes a number of American State Prisons.

The following criteria are established according to the "Cutter system of plasmapheresis" on file with EOB:

1. Suitability of the donor.
2. Immunization

3. Donor follow-up

4. Phlebotomy; preparation of phlebotomy site, type and quantity of anti-coagulant, collected blood volume and frequency of donation.

5. Method of handling blood from bleeding to beginning of processing - cell removal, plasma pooling and storage temperature (plasma kept in frozen state).

4.2.2. AHF Production process

A flow diagram and details of manufacturing procedure are given.

Cryoprecipitate is recovered by centrifugation from thawed pools of fresh frozen human plasma. Soluble proteins are removed by washing and the AHF proteins extracted. Extraneous non-AHF protein is removed by pH and temperature adjustment. Prothrombin complex proteins are removed by adsorption with $Al(OH)_3$. The AHF activity is concentrated by alcohol precipitation.

The bulk solution is clarified after pH adjustment and additional buffer added to bring the concentration to 25-30 units of Factor VIII/ml and further clarified by membrane filtration. 1% dextrose is added and the bulk sterile filtered and filled aseptically as 10 and 20 ml aliquots in final containers which are plugged, frozen and freeze-dried. The final containers are stored at 5°C.

5. QUALITY CONTROL

5.1 Bulk active substance

The following tests are carried out on liquid bulk before filling:

1. Absorbance at 280 mμ. No limits are given for the spectrophotometer tests.
2. Total nitrogen
3. Non-protein nitrogen
4. Factor VIII potency
5. pH

5.2 Final product

The specification of the final product is as follows:

Factor VIII (Potency)	NLT 10 Units AHF/ml when reconstituted with 10 ml or 20 ml distilled water as on page 9-1a
Specific Activity	NLT 0.2 U/mg Protein
Thrombin	No clotting in less than 6 hours.
Moisture	NMT 2%
pH	6.40 - 7.40
Na^+	145 - 185 mEq/L
Cl^-	125 - 160 mEq/L
Al^{+++}	NMT 1 ppm
Solubility & Clarity	NMT 30 minutes at 30-35°C
Dextrose	0.85 - 1.15%
Safety	To pass test (attached)
Pyrogen	To pass test (attached)
Identity	To pass test (attached)
a. Potency	NLT 10 Units AHF/ml when reconstituted with 10 ml or 20 ml distilled water as on page 9-1a
b. Precipitin Test	
Human	Positive
Bovine	Negative
Equine	Negative
Sterility	To pass test (attached)
Depressor Substances	To pass test (USP XVIII Dose 25 u/kg)

The specific activity of the Factor VIII is not less than 200 units per gram of protein and on reconstitution the following additives are present:-

Glycine	0.25 M
Sodium chloride	0.15 M
Sodium citrate	0.01%
Dextrose	1%

Details of the quality control tests are given including preparation of the house standard together with comparisons between it and the NIH standard. Dr Bangham may wish to comment on these. Safety, pyrogen, identity and sterility tests are done in accordance with the biological product regulations submitted. (U S A)

Protocols of the quality control findings of 6 different batches of Koate without dextrose and of another 6 batches containing 1% dextrose are given. These appeared to be satisfactory and show consistency of manufacture.

6. STABILITY

6.1 Proposed shelf life

1 year at 2-8°C from date of last valid potency assay.

6.2 Stability data

12 different lots (6 with dextrose and 6 without dextrose) have been stored at 5°C and 25°C. There were some anomalous findings but on the whole the results indicate no deterioration of the product containing dextrose when stored at 5°C for 1 year. Reasonable explanations have been offered for some of the inconsistencies and the increase of AHF activity may have been due to deterioration of some AHF on storage or an activation phenomenon. It should be noted that the storage temperature claimed is 2-8°C and that the tests were carried out at 5°C.

7. EVIDENCE OF EFFICACY

The following clinical experience is reported:

7.1 Clinical evaluation of Koate by 5 investigators, Abildgaard et al.

7.2 The in vivo longevity of anti-haemophilic factor, Abildgaard et al.

7.3 Assay of plasma anti-haemophilic globulin, Pool and Robinson

7.4 Use of high potency Factor VIII fractions, Abildgaard.

7.5 Summary of accumulative clinical experience

1. The clinical evaluation of Koate™ was carried out in 33 patients who were administered a total of 166 infusions. During this evaluation, the half-life and in vivo recovery of Koate™ were determined, and clinical efficacy and safety were demonstrated.

2. Biologic half-life of the product averaged 12.7 ± 1.0 hours, which corresponds closely to the factor VIII half-life reported in the literature. The initial 50% disappearance averaged 5.1 ± 0.4 hours.

3. In vivo recovery of the infused Koate™ averaged 107 ± 3%, which demonstrates a good recovery of the material infused.

4. A dose-response relationship was demonstrated between the amount of Koate™ infused and the levels of activity attained 10 to 15 minutes post-infusion. These data indicate that one unit of Koate™ will cause an average in vivo increase of 2.3 ± 0.1% as measured 10 to 15 minutes after infusion.

Dose, units/kg	Post-infusion Increase of Factor VIII Activity, % of Normal	NO: Infusions
15	27 ± 1	73
15-29	48 ± 3	61
30-44	90 ± 11	25
45-60	92 ± 8	7

5. Koate™ was hemostatically effective in 22/22 patients treated with 109 infusions for acute bleeding episodes.

6. Koate™ was effective in preventing bleeding during surgery and in the postoperative healing period in 5/5 patients.

7. Home infusion was successfully employed for 5/5 patients who were administered a total of 30 infusions at home. The average dose of Koate™ administered to treat early bleeds was 12.5 ± 0.9 units/kg.

8. Only two side effects were reported during the clinical evaluation of Koate™. Beginning 20 minutes after infusion, one patient had transient chest discomfort and cough for one hour. He subsequently had twelve more infusions of Koate™ without incident. Another patient had transient dizziness following each of eight infusions. No cases of serum hepatitis were reported following treatment with Koate™. In addition, no reports have been received attributing hepatitis to Koate™ since its introduction in the U S A in February 1974. However, attached is a copy of a letter from Kasper and Kipnis in the JAMA 221:510,1972 regarding hepatitis and clotting factor concentrates, such as this product. It is one of the references used in the package insert.

9. No fibrinolytic split products, which are proteolytic degradation products of fibrinogen and fibrin associated with anticoagulant properties, were found in post-infusion serum samples from six patients.

10. Serum haptoglobin levels measured before and after infusion in four patients were the same, indicating that at a maximum dose of 43 units/kg Koate™ there was no hemolysis due to the presence of anti-A and anti-B in Koate™.

11. The biologic half-life, in vivo recovery and efficacy did not vary from lot to lot of Koate™.

12. All five investigators reported similar results. The biologic half-life reported was 16.4 ± 2.0, 11.1 ± 0.9, 11.2 ± 1.8 and 6.5 hours. In vivo recovery was 108 ± 3%, 98 ± 5%, 93 ± 8%, 118 ± 13% and 90%. Satisfactory hemostasis was achieved in all patients treated.

13. All of the six lots of Koate™ tested clinically were equally safe and effective, including the two lots that contained dextrose to increase solubility.

14. In conclusion, Koate™ has been demonstrated to be a safe and efficacious preparation for treating or preventing bleeding in hemophilic patients with factor VIII deficiency.

8. MEDICAL COMMENT

This Factor VIII preparation would appear to have been adequately prepared and to be efficacious in clinical usage. It suffers from being prepared from

multi-centre donations which cannot be properly controlled by inspection. Nevertheless each individual donation is said to be tested by radioimmuno assay and that the control of the blood donations is in accordance with the latest FDA regulations, copies of which are not included in the submission. The information set out is superior to that originally offered by Travenol but in fairness it is believed that Travenol have improved their method of manufacture in accordance with the new FDA regulations.

In the past the Committee have recommended that the following conditions are accepted:

1. Information is provided on:-

   (a) The number of donations from which plasma is pooled for the manufacture of the product.

   (b) The reasons for, and rate of, rejection of donors or donations, centre by centre.

2. The potency is expressed in international units and in addition, further details are provided relating to the method of assay; the standard used and its calibration: and on batch reproducibility.

3. The product is stored at a temperature of 6°C or below.

4. Product labelling complies with the BP.

5. The batch release procedure shall apply.

9. RECOMMENDATION

Subject to quality control being considered satisfactory and to confining the expiry date to storage at 5°C the Committee might feel that a Product Licence could be granted.

17.12.75

R D Andrews