ANTIHAEMOPHILIC FACTOR (HUMAN)

License Submission - Revised

3/9/83

PL 1605/0004 U.K.

PART I - Application Form

Form MLA 201 obtainable from Medicines Division should be used for this part

MEDICINES ACTS 1968 and 1971 - APPLICATION FOR PRODUCT LICENCE

1. Name of Product: If the marketing name is not yet settled, give another (possibly temporary) name by which the product can be identified. Antihemophilic Factor (Human) KOATE ™

2. (i) Full name and address of proposed licence holder: Miles Laboratories, Ltd.
Stoke Court, Stoke Poges, Slough SL2 4LY, England

The licence could be held by individuals or by legal persons such as Limited Companies. In the latter case the company's full legal style, registration number and registered address should be stated here. If some other title (eg a division of the company) is to be shown on the licence it should be shown against trading style

(ii) Address for correspondence if different from above:

3. Trading style to be shown on licence if different from above:

4. Role of proposed licence holder: (See paragraph 3.3 of the Guide to the Licensing System - MAL 1).

~~(i) as person responsible for composition of product manufactured in UK.~~
(ii) as person who imports or procures its importation.
~~(iii) as person who first sells or supplied it as a medicinal product.~~

5. Activities for which licence is required:

Delete amend or add as necessary

(i) selling or supplying product in the UK.
(ii) procuring the manufacture or assembly of the product for sale or supply in the UK.
(iii) importing or procuring the importation of the product.
(iv)

6. Applicant's own reference no: 1605

7. Details of earlier applications: (ie under Medicines Act or earlier voluntary scheme, successful or not)
- give reference number -
PLA 1605/0004 Antihemophilic Factor (Human)

8. To cover sale and supply of the product manufactured before the grant of the licences: XXX/NO

9. Scientific Evidence:

(i) Chemistry and Pharmacy — Pages
(ii) Experimental and Biological Studies — Pages
(iii) Clinical Trials — Pages

Insert number of pages in each part.

10. Number of pages of product particulars - Part IA — Give numbers of pages in Part IA

11. I/we apply for the grant of a product licence to the proposed holder named above in respect of the Product(s) to which the Product Particulars on Page 2 refer and in accordance with the other particulars annexed; the said licence to be for a period of five years and subject to the following provisions-

11.1. All the Standard Provisions appicable to product licences under regulations for the time being in force under Section 47 of The Medicines Act 1968.

11.2. The product shall not be recommended to be used for any purpose other than those specified in the Product Particulars as Uses and shall be sold or supplied in accordance with the said Product Particulars except in so far as say from time to time be approved by the licensing authority.

11.3. The specification of the constituents and of the finished product shall be in accordance with the information contained in or furnished in connection with the application.

11.4. The product is to be manufactured only in accordance with the methods set out in this application or furnished in connection with it.

11.5. No material information has been omitted (within the knowledge of the signatory).

Date .....

Signature .....

State capacity in which signed

Product Particulars

1. Name of Product: Antihemophilic Factor (Human) Koate™

   If the marketing name is not settled this should be left blank and the name notified later as available.

2. Pharmaceutical form: A sterile lyophilized powder for reconstitution with sterile water for injection for intravenous use.

   Describe the pharmaceutical form eg tablets, capsules, injections, and state whether the product is (a) in a form for administration to human beings: or (b) for use as an ingredient in preparing medicinal products.

3. Active constituents: Supplied as vials containing approx. 250,500,1000 or 1500 units of Factor VIII together with a suitable volume of Sterile Water for Injection USP and a sterile filter needle.

   Indicate the way in which the active ingredients and quantities will be declared on any leaflet, label or descriptive material. Each constituent should be described under (a) its approved name or monograph name: or (b) where there is no approved name or monograph name the non-proprietary designation or other descriptive appellation by which it can be readily identified: or (c) the trade name in other cases.

4. Uses: For the treatment of classical haemophilia (haemophilia A) in which there is a demonstrated deficiency of the plasma clotting factor, Factor VIII. See also package insert (attached).

   State recommended clinical use the proposed route(s) of administration and any directions for use to be included in labels and leaflets.

5. Recommended dose and dosage schedule: See package insert (attached) Attachment 1

   State the recommended dosage for: See package insert (attached) Attachment 1
   (i) adults and if appropriate (ii) children and infants by age groups. Where appropriate, distinguish between therapeutic and prophylactic doses and between dosages recommended for different clinical uses.

6. Contraindications, Precautions and Warnings: See package insert (attached)

   State particulars of contraindications, warnings and precautions to be included in the data sheet, container label, package label or any leaflets.

7. Method of retail sale or supply: By direct government contract and private sale.

   State whether it is proposed to make the product available:
   (a) for general sale: or (b) only through registered pharmacies - (i) for over the counter sale: or (ii) as a prescription item or (c) through some other specified group of outlets eg hospitals, specialised clinics laboratories from automatic machines or herbal practitioners

8. Manufacturer of dosage form: Cutter Laboratories, Division of Miles Laboratories, Inc.
   Fourth & Parker Streets, Berkeley, Ca. 94710 U.S.A.

   State the name(s) and address(es) of the manufacturer(s) of the dosage form.

Applicants reference number (as on page 1) 1605

Applicants signature.....

MAL 2 Part IB Supplementary Details

1. Product Literature

1.1 Labeling and Package Inserts

Attachment 1 consists of copies of labeling and package insert.

1.2 Data Sheets

Attachment 2 is a copy of the proposed data sheet.

2. Background

2.1 Applications in Other Countries

Koate is licensed in the following countries:

Austria
Argentina
Brazil
Canada
Chile
Costa Rica
Dominican Republic
Ecuador
El Salvador
Germany
Greece
Guatemala
Ecuador
El Salvador
Hong Kong
Indonesia
Iran
Israel
Italy
Japan
Kuwait
Lebanon
Mexico
Nicaragua
Pakistan
Panama
Peru
Philippines
Puerto Rico
Taiwan
United Arab Emirates
Venezuela

2.2 Background

The development work was carried out some years ago, but the techniques have been updated.

3. Persons Involved in the Manufacture of the Finished Products and their Distribution in the U.K.

3.1 Manufacturer and Assembler

The manufacturer is Cutter Laboratories, Division of Miles Laboratories, Inc. at two locations:

Berkeley, California
Clayton, North Carolina

3.2 Arrangements for Storage

Marie please supply this information

3.3 Importer

Marie, please supply this information

3.4 Responsibility for Quality Control

a) The manufacturer will supply test data attesting that the product is suitable for release for marketing and he will be responsible.
b) Quality control will be carried out by manufacturer at site of production.

MAL 2 Part II Pharmaceutical Data in the Dosage Form

1. Finished Product

1.1 Description

Antihaemophilic Factor is a sterile, stable, purified, dried concentrate containing Factor VIII. Sterile Water for Injection is supplied as reconstituting fluid, as well as a sterile filter needle.

1.2 Complete Formula

1.2.1. Active Constituents

Coagulation Factor VIII (not less than 0.2 units of Factor VIII/mg protein).

250 unit/10 ml fill	not less than 250 u/vial
500 unit/20 ml fill	not less than 500 u/vial
1000 unit/30-40 ml fill	not less than 1000 u/vial
1500 unit/30-40 ml fill	not less than 1500 u/vial

1.2.2. Other Constituents

a. Chloride (125-160 mlEq/l)

250 unit	88.5 - 113.3 mg/vial
500 unit	117.0 - 226.6 mg/vial
1000 unit	354.0 - 453.2 mg/vial
1500 unit	354.0 - 453.2 mg/vial

b. Sodium (145-185 mEq/l)

250 unit	66.4 - 84.73 mg/vial
500 unit	132.8 - 169.46 mg/vial
1000 unit	263.6 - 338.92 mg/vial
1500 unit	263.6 - 338.92 mg/vial

c. Water for Injection

250 unit	10 ml
500 unit	20 ml
1000 unit	30/40 ml
1500 unit	30/40 ml

1.2.3. Overage

An overage of 2% is used as described in USP XX, p. 862, to allow recovery of labeled activity.

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1.3 Containers

SPECIFICATIONS FOR CONTAINERS AND CLOSURES

A. Antihemophilic Factor (Human), Koāte®

Bottle 1500 units 100 ml., U.S.P. Type I or Type II clear glass

Bottle (1000 units): 100 ml., U.S.P. Type I or Type II clear glass

Bottle (500 units): 50 ml., U.S.P. Type I or Type II clear glass

Bottle (250 units): 30 ml., U.S.P. Type I or Type II clear glass

Stopper: Gray 20 mm., prime stock, natural, sulfur-free, non-oxidizing, non-toxic rubber.

Seal: Aluminum 20 mm., ~~clear lacquered outside or~~ West Plastic Flip-Off Seals

B. Sterile Water for Injection, U.S.P. [Diluent for Antihemophilic Factor (Human) - Koāte®]

Bottle (40 ml. fill): 50 ml., U.S.P. Type I or Type II clear glass

Bottle (20 ml. fill): 30 ml., U.S.P. Type I or Type II clear glass

Bottle (10 ml. fill): 20 ml., U.S.P. Type I or Type II clear glass

Stopper: Gray 20 mm., prime stock, natural, sulfur-free, non-oxidizing, non-toxic rubber.

Seal: Aluminum 20 mm., ~~clear lacquered outside or~~ West Plastic Flip-Off Seals

C. Filter Needle for Reconstitution

Cannula: 16 gauge x 3/4" stainless steel

Hub: Aluminum with standard Luer taper with Luer-Lok feature.

Filter: 100 mesh stainless steel

Assembly: Overall length 1-1/4 ± 1/16"

1.4 Formulation Used in Clinical Trials

Same as in 1.2 above.

2. Manufacture of Drug Form

2.1 Manufacturing Formula

Cryoprecipitate is recovered by centrifugation from thawed pools of fresh frozen human plasma. Soluble proteins may be removed by a wash of the cryoprecipitate. Extraneous non AHF protein is removed through pH and temperature adjustment. Prothrombin complex proteins are removed by adsorption with $Al(OH)_3$. The AHF activity is concentrated by alcohol precipitation or ultrafiltration.

2.2 Manufacturing Process

Manufacturing Procedure

1. Fresh frozen plasma is thawed at NMT +5° C and warmed to NMT 15° C before chilling to 3° ± 3° C where it is held for NMT three hours. The insoluble cryoprecipitate is collected by centrifugation at NMT 10° C.

2. The cryoprecipitate may be diced and washed (NMT 10 l/kg) with buffer (approximately 0.005M sodium citrate, 0.075M NaCl, pH 6.4 ± 0.1) at 2.5° ± 2.5° C for approximately 30 minutes.

2A. The cryoprecipitate, either washed or not, may be prepared for bulk sale by dispensing into plastic containers and storing at -20° C or colder until shipment.

3. The cryoprecipitate is extracted at 32° ± 5° C for NMT two hours with NMT 10 l/kg of WFI.

4. The solution is adjusted to pH 6.8 ± 0.2 then chilled to 5° ± 2° C. The precipitate which forms is removed by decantation or centrifugation at 5° ± 2.5° C.

5. The supernatant is treated for approximately 30 minutes at 5° ± 2.5° C with an amount of 1 to 3% $Al(OH)_3$ suspension in WFI sufficient (2 to 5 ml/l A_{280} unit) to remove contaminating prothrombin complex. The adsorbed $Al(OH)_3$ is removed by filtration and/or centrifugation at 5° ± 2.5° C.

(The clear effluent is processed by step 6 through 8 (alcohol precipitation process) or, optionally, by steps 6A through 8A (ultrafiltration process).)

6. The clear effluent is adjusted to pH 6.9 ± 0.2 after adjusting the salt concentration to approximately 0.01M sodium citrate and 0.15M NaCl. Cold (-15° C or colder) 95% ethyl alcohol (SDA-3A) is added to achieve a final concentration of 20 to 25% while the temperature is lowered to NMT +2°C.

7. After approximately one hour mixing, the precipitated proteins are removed by centrifugation at NMT +2°C.

8. The recovered paste is dissolved in a citrated-saline with glycine buffer. The solution may be frozen and stored frozen at -25°C or colder. The fresh or thawed solution is adjusted to a pH value of 6.9 ± 0.5. Prior to clarification, dextrose may be added. The clarified solution is diluted with additional buffer and further clarified through a series of membrane filters, or the equivalent, graduated in porosity. The clarified solution may be frozen, stored and thawed before further processing.

6A. The clear effluent is concentrated using an Amicon/Romicon Hollow Fiber, or equivalent ultrafilter equipment to an A_{280} of approximately 40 ± 20; citrate, saline, and glycine are added, the pH adjusted to 6.9 ± 0.5, and may be held frozen at -25°C or colder prior to thawing for bulk production.

7A. The concentrate is clarified as necessary and the pH is adjusted to 6.9 ± 0.5.

8A. Prior to clarification, dextrose may be added. The clarified solution is diluted with additional buffer in order to adjust the AHF potency to the desired range and further clarified through a series of membrane filters, or the equivalent, graduated in porosity. The clarified solution may be frozen, stored and thawed before further processing.

9. The clarified solution is then sterilized by filtration through a 0.22 micron porosity membrane filter or its equivalent. Dextrose may be added if not added prior to clarification. The filter rinse may be concentrated by ultrafiltration.

2.3 Assembling Procress

The sterile bulk solution is aseptically filled and frozen at -30°C or colder. The product is lyophilized in vacuo by slowly increasing the temperature from -30°C or colder to NMT +37°C. The final containers are stored at 2 to 8°C.

The containers are labeled and placed into unit cartons along with the sterile filter needle and direction insert.

Quality Control

See Attachment 3 MAL 41.

3.1 Specifications of Constituents

3.1.1 Constituents Complying with Pharmacopoeial Monographs.

Complying with specifications detailed in USP XX/NFXV are the following constituents:

Sodium Chloride USP
Acetic Acid USP
Sodium Citrate USP
Sodium Hydroxide USP
Hydrochloric Acid USP
Alcohol, SDA-3A USP

3.1.2 Constituents Not in a Pharmacopoeia

Attachment 4 lists the constituents and their specifications.

Source Plasma (Human)
Aluminum Hydroxide Gel

3.1.3 Suppliers of Active Ingredients

Attachment 5 (QAPS 003) lists the approved suppliers of Source Plasma (Human). They are licensed by the FDA and inspected by the FDA and by Cutter Laboratories to ensure compliance with correct procedures and record keeping.

3.2 In-Process Control

3.2.1 Analytical Control

a. All units of plasma are tested and found negative for HB_sAg.

b. Attachment 6 (QAP 510), In-Process and Finished Product Inspection.

c. Since this is a continuous process, the in-process controls consist of constant monitoring of temperature, pH, etc.

3.2.2 Sampling for Quality Control

Since the manufacturing process is a rapid and continuous one, samples are not taken for quality control.

3.3 Finished Product Specifications

3.3.1 Tests and Limits Applied

Attachment 7 is a copy of the final product specifications, the tests and the limits for each test.

3.3.2 Analytical Methods

Attachment 8 is the Manual of Methods. It contains the various procedures used in connection with this product and will be referred to throughout this submission.

4. Development Pharmaceutics and Biological Availability

Factor VIII is very labile and procedures were developed to obtain a reasonable separation and concentration as expeditiously as possible. Dextrose is added to reduce the time of reconstitution. Since the product is injected intravenously, it is immediately bio-available.

5. Stability

5.1 Batches Examined

Lot Nrs. NC 8122, NC 8115, 8114

5.2 Conditions of Storage

These are indicated in the stability report.

5.3 Containers

Stability tests are done on product in final containers as described in 1.3 above.

5.4 Analytical Methods

The methods used are contained in Attachment 8 , the Manual of Methods.

5.5 Results

Attachment 9 contains the results of the stability testing.

5.6 Discussion of Results

The results shown in Attachment 9 indicate the product is stable for the parameters tested, including the specifications for the final product.

5.7 Proposed Shelf Life

The shelf life is two years when stored at 2°-8°C. We have data showing the product is stable beyond this period.

5.8 Storage Conditions, user instructions and pharmaceutical precautions.

Storage Conditions

"Store at 2°-8°C (35°-46°F). Do not freeze. Storage of lyophilized powder at room temperature (up to 25°C (77°F) for six months, such as in home treatment situations, may be done without loss of Factor VIII activity."

User instructions

INDICATIONS AND USAGE

Koāte is indicated for the treatment of classical hemophilia (hemophilia A) in which there is a demonstrated deficiency of activity of the plasma clotting factor, Factor VIII. Koāte provides a means of temporarily replacing the missing clotting factor in order to correct or prevent bleeding episodes or in order to perform emergency and elective surgery on hemophiliacs.

Antihemophilic Factor (Human) is not effective in the treatment of von Willebrand's disease.

DOSAGE

Each bottle of Koāte has the AHF activity in AHF/IUs stated on the label of the bottle. One AHF unit is equivalent to one International unit.

Abildgaard, et al[11] have reported from studies in hemophilic children a linear dose-response relation with an approximate yield of 2% rise in Factor VIII activity for each unit of Factor VIII per kg of body weight transfused. Clinical experience with Koāte has demonstrated an essentially identical dose-response relationship.[12] Therefore, the following formulae provide a guide for dosage calculations:

Expected Factor VIII increase (in % of normal) =

$$\frac{\text{AHF/IU administered} \times 2.0}{\text{body weight (in kg)}}$$

AHF/IU required = body weight (kg) x desired Factor VIII (% normal) x 0.5

It should be emphasized, however, that all efforts should be made to follow the course of therapy with Factor VIII level assays. It may be dangerous to assume any certain level has been reached unless direct evidence is obtained.

RECONSTITUTION AND ADMINISTRATION

1. Warm unopened diluent (Sterile Water for Injection, USP) and Koāte to room temperature, but not higher than 37°C (99°F).

2. Remove the plastic flip-top caps from both bottles to expose the central portions of the rubber stoppers and cleanse each stopper with suitable antiseptic immediately before each piercing. We recommend the following procedure: First swab the stopper with Iodine Tincture, USP followed by a sterile antiseptic swab.

3. With a sterile needle and syringe withdraw the appropriate volume of diluent and transfer to the bottle of lyophilized Koāte. The Koāte bottle is not sealed under vacuum. Add the Sterile Water for Injection, USP diluent gently so as to avoid excessive foaming. Do not bleed out air either before or after reconstitution.

4. Withdraw needle from the concentrate bottle stopper and gently agitate the bottle from time to time until the Koāte powder is completely dissolved. Reconstitution usually requires less than 5 minutes.

5. After the concentrate powder is completely dissolved, withdraw the Koāte solution into the syringe through the filter needle which is supplied in the package. Replace the filter needle with an appropriate sterile injection needle, e.g., 21 gauge x 1 inch, and inject intravenously.

6. If the same patient is to receive more than one bottle of Koāte, the contents of two bottles may be drawn into the same syringe through filter needles before attaching the vein needle. Additional bottles may be drawn into the same syringe through filter needles supplied.

Pharmaceutical Precautions

CONTRAINDICATIONS

There are no specific contraindications to the use of Antihemophilic Factor (Human).

WARNING

Koāte concentrate is a purified dried fraction of pooled plasma obtained from many paid donors. The presence of hepatitis viruses should be assumed and the hazard of administering Koāte concentrate should be weighed against the medical consequence of withholding it, particularly in persons with few previous transfusions of blood or blood products.

Kasper and Kipnis[4] have concluded that those who have had little exposure to blood products have a high risk of developing hepatitis after introduction of clotting factor concentrates, such as this product. For those patients, especially those with mild hemophilia, they recommend single donor products. However, for patients with moderate or severe hemophilia who have received numerous infusions of blood or blood products, they feel that the risk of hepatitis is small. They believe that the clotting factor concentrates have so greatly improved the management of severe hemophilia that these products should not be denied to appropriate patients.

PRECAUTIONS

1. Koāte is intended for treatment of bleeding disorders arising from a deficiency in Factor VIII. This deficiency should be proven prior to administering Koāte, since no benefit may be expected from its use in treating other causes of hemorrhage.

2. After reconstitution, administer promptly (within 3 hours). Do not refrigerate after reconstitution. NOTE: The recommendation to administer promptly after reconstitution is intended to avoid the ill effect of any possible bacterial contamination occurring during reconstitution. Koāte is fully stable, without potency loss for at least 24 hours at room temperature after reconstitution.

3. Administer only by the intravenous route.

4. A filter needle should be used prior to administering.

5. Koāte contains levels of blood group isoagglutinins which are not clinically significant when controlling relatively minor bleeding episodes. When large or frequently repeated doses are required in patients of blood groups A, B or AB, the possibility of intravascular hemolysis should be considered.

6. Administration equipment and any reconstituted Koāte not used should be discarded.

ADVERSE REACTIONS

Allergic reactions may result from the administration of AHF preparations including chills, fever, and hypersensitivity reactions.[5,6]

When large or frequently repeated doses are required in patients of blood groups A, B or AB, there is a possibility of intravascular hemolysis.[7-9] Should this condition occur leading to progressive anemia, administration of type O packed red blood cells should be considered.[7] Also the administration of type specific cryoprecipitate has been recommended for maintaining adequate Factor VIII levels.[8] Massive doses may also result in hyperfibrinogenemia.[10]

The risk of hepatitis is present with the administration of AHF concentrate preparations (see discussion under WARNING).

5.9 Ongoing Stability Trials

The product has been licensed and marketed in the U,S. for approximately 10 years. The shelf life has been supported. Cutter Laboratories conducts ongoing stability studies to support extended shelf-life.

6. Containers

6.1 Type of Container

The same container used in final product was used in the stability studies. They are described in 1.3 above.

6.2 Packaging Inclusions

None

Part II Addendum; Chemistry of the Drug Substances

The drug substance is a fraction of normal human plasma and is not a new drug substance. This section is not applicable.

Part III Experimental and Biological Studies

The drug substance is not a new drug substance since it is a fraction of normal human plasma. The pharmacology and pharmacokinetics are those of the fraction VIII found in normal human plasma.

Part IV Studies in Humans

The product is a well established one and is found in several pharmacopoeiae. The studies in humans are found in Attachment 10 . The product has been used in humans for more than 10 years since licensure by the FDA. It has been shown to be safe and effective.