Antihemophilic Factor (Human)

Koate™

Product Licence Application (Abridged)

File 1

SUPPLEMENTARY PARTICULARS

MASTER COPY

Bayer

Bayer UK Limited
Pharmaceutical Division
Haywards Heath Sussex RH16 1TP

BAYER UK

Ph Application

OCT 1975

ANTIHEMOPHILIC FACTOR (HUMAN) KOATE™

INDEX TO SUBMISSION

/Continued

Antihemophilic Factor (Human) Koāte™

Index (Continued)

MEDICINES ACT 1968 and 1971 - APPLICATION FOR PRODUCT LICENCE

MLA 201
Page 1

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

1.2. Full name and address of proposed licence holder:

Bayer UK Limited
Bayer House
Richmond
Surrey
TW9 1SJ

Registered company no. 935048

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

Bayer UK Limited
Pharmaceutical Division
Haywards Heath
West Sussex RH16 1TP
(Correspondence to be sent to this address).

1.4. Role of proposed licence holder:

~~(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 supplies it as a medicinal product.~~

1.5. Activities for which licence is required:

(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)

1.6. Applicants own reference no:

1.7. Details of earlier applications: Not applicable

1.8. To cover sale and supply of the product manufactured before the grant of the licence: ~~YES/~~NO

1.9. Scientific Evidence:

(i) Chemistry and Pharmacy — Pages 98
(ii) Experimental and Biological Studies — Pages Not applicable (ii)
(iii) Clinical Trials — Pages 52

1.10. Number of pages of supplementary information: 21

1.11. 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 -

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

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 may from time to time be approved by the licensing authority.

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.

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

5. The number of the licence shall appear on all containers or packages in which the product is packed and on any package inserts or accompanying literature.

Date 16/10/1975

Signature GRO-C

State capacity in which signed GRO-C

For licensing authority use

Product Particulars

2.1 Name of Product: Antihemophilic Factor (Human) Koate™

2.2 Pharmaceutical form: A sterile lyophilised powder for reconstitution with sterile water for injection for intravenous use.

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

2.4 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).

2.5 Recommended dose and dosage schedule: See package insert (attached)

2.6 Contra-indications, Precautions and Warnings: See package insert (attached)

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

2.8 Manufacturer of dosage form: Cutter Laboratories Inc.
Berkeley
California 94710
USA.

Applicants reference number (as on page 1)

Applicants signature. GRO-C

3. Supplementary Particulars

3.1 Physical characteristics

Not applicable.

3.2 Manufacture

(a) Cryoprecipitate is recovered by centrifugation from thawed pools of fresh-frozen human plasma. Soluble proteins are removed by a wash of the cryoprecipitate and AHF proteins extracted. Extraneous non-AHF protein is removed through pH and temperature adjustment. Prothrombin complex proteins are removed by adsorption with aluminium hydroxide. The AHF activity is concentrated by alcohol precipitation. The bulk solution is freeze-dried in the final containers under aseptic conditions.

(b) Cutter Laboratories Inc., Berkeley, California 94710, USA.

(c) As above.

(d) The product is stored at 2-8°C in a refrigerator in our warehouse at Haywards Heath.

3.3 Quality Control

(a) Quality control will be exercised by Cutter Laboratories

(b) The decision that any batch of the product is of an acceptable quality for marketing is taken by Cutter.

3.4 Containers

(i) Antihemophilic Factor (Human) - Koāte™

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

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

Stopper: Gray 20 mm, prime stock, natural, sulphur-free, non-oxidising, non-toxic rubber. Durometer hardness 42 ± 5°.

Seal: Aluminium 20 mm, clear lacquered outside.

3.4 (continued)

(ii) Sterile Water for Injection, USP (Diluent for Antihemophilic Factor (Human) - Koāte™)

Bottle (20 ml fill): 30 ml, USP Type I clear glass.

Stopper: Gray 20 mm, prime stock, natural sulphur-free, non-oxidising, non-toxic rubber. Durometer hardness 45 ± 5°.

Seal: Aluminium 20 mm, clear lacquered outside.

(iii) Filter Needle for Reconstitution

Cannula: 16 gauge x 3/4" stainless steel.

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

Filter: 100 mesh stainless steel.

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

To be stored at 2-8°C.

3.5 Labelling

Copies of labels and the package insert are attached. The expiry date stated on the label is one year from the date of the last valid potency assay.

3.6 Importation

The licence holder is the actual importer of the product.

3.7 Applications in Other Countries

Koāte has been passed by the F.D.A. for marketing in the U.S.A. We are awaiting further information concerning this.

3.8 Scientific Evidence

Detailed information is supplied on Chemistry and Pharmacy and Clinical Trials.

PACKAGE INSERT

This will be overprinted with our name, Bayer UK Ltd., Pharmaceutical Division, address, Haywards Heath, Sussex, and the product licence number.

Antihemophilic Factor (Human)

Koāte™

SEE SECTIONS ENTITLED "INDICATIONS" AND "WARNING"
FOR DESCRIPTION OF HEPATITIS RISK

DESCRIPTION

Antihemophilic Factor (Human), Koāte™ is a stable, purified, dried concentrate of human Antihemophilic Factor (Factor VIII, AHF, AHG) intended for use in therapy of classical hemophilia (hemophilia A). Koāte™ is purified from the cold insoluble fraction of pooled fresh frozen plasma by modification and refinements of the methods first described by Hershgold, Pool and Pappenhagen(1). Koāte™ contains Factor VIII in concentrated and in highly purified form being some 40 to 170 times purified over whole plasma, and containing minimal quantities of fibrinogen. Consequently Koāte™ is a highly potent source of Factor VIII activity, containing approximately 25-30 times as much Factor VIII as an equal volume of fresh plasma. Relatively small volumes of Koāte™ are needed to raise significantly the circulating level of Factor VIII. For example, 500 clinical units of Factor VIII (equivalent to 500 ml of fresh frozen plasma) can be administered in a volume of only 20 ml containing a total protein of about 0.5 grams. The final product, when reconstituted as directed, will contain 1% Dextrose (anhydrous) U.S.P.

Hemophilia A is an hereditary bleeding disease characterized by deficiency activity of a specific plasma protein clotting factor, Factor VIII. The disease is sex linked being transmitted by females but occurring almost exclusively in males. In individuals so afflicted, the reduced level of Factor VIII may be sufficient so that hemorrhage can occur spontaneously or after only minor trauma. Surgery on such persons is not feasible without first correcting the clotting factor abnormality.

The medical management of hemophiliacs is based on replacement to the circulation of the blood clotting factor which is deficient or absent. Prior to the availability of clotting factor concentrates, this was accomplished by transfusions of blood, fresh plasma or fresh frozen plasma. The effectiveness of these infusions is limited by the large volumes required to achieve and maintain hemostasis. The blood volume becomes expanded because of protein overload; cerebral edema, pulmonary edema, and cardiac embarassment may result(2,3).

Because of these limitations, much effort has been expended by a number of investigators in separating and concentrating Factor VIII from plasma in a form suitable for substitution therapy in Hemophilia A patients. A number of concentrate preparations of varying degrees of purification have evolved and have been used with clinical success. Koāte™ is a

highly purified potent concentrate which can be effectively used to increase the Factor VIII levels of patients to normal or near normal values without circulatory overload. Antihemophilic Factor (Human), Koāte™, offers many advantages over whole blood, plasma, single unit cryoprecipitate or less potent concentrates. Among the most significant of these are:

1. Higher potency Factor VIII than cryoprecipitate or other available concentrate preparations. Therefore, adequate Factor VIII can be supplied with relatively smaller amounts of fibrinogen and other non Factor VIII proteins. This is particularly important when high circulating levels of Factor VIII must be maintained for prolonged periods, or where inhibitors must be overcome.

2. Each lot of Koāte™ is assayed and labeled for its Factor VIII content. This permits more precise estimation of dose and prediction of effects.

3. As a lyophilized dry product, Factor VIII is stable in contrast to its marked decay in stored plasma.

4. Koāte™ reconstitutes rapidly and easily and does so without excessive shaking and foam formation which can inactivate Factor VIII.

5. Being of human origin there is no danger of species antigenicity as occurs with concentrates from bovine or porcine source.

6. The high Factor VIII potency in the reconstituted product allows intravenous infusion by direct syringe injection or drip infusion without significant reactions. This permits office and home treatment.

7. Koāte™ is free of thrombin, thromboplastin-like activity, depressor activity, and contains relatively low levels of anti-A - anti-B blood group isoagglutinins (see discussion under Precautions). It is free of heparin and no heparin need be added before its use.

THIS PRODUCT IS PREPARED FROM UNITS OF HUMAN PLASMA WHICH HAVE BEEN TESTED AND FOUND NON-REACTIVE FOR HEPATITIS ASSOCIATED (AUSTRALIA) ANTIGEN. UNFORTUNATELY THIS TEST DOES NOT WITH CERTAINTY PRECLUDE THE PRESENCE OF HEPATITIS VIRUS. SEE WARNING.

ACTION

Antihemophilic Factor (Human) is a plasma protein which corrects the coagulation defect of patients with classical hemophilia (hemophilia A). It is needed for the formation of prothrombin to thrombin by the intrinsic pathway.

INDICATIONS

Antihemophilic Factor (Human), Koāte™, is indicated for the treatment of classical hemophilia (hemophilia A), in which there is a demonstrated deficiency 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.

CAUTION: BECAUSE OF THE POSSIBILITY THAT ANY LOT OF KOĀTE™ MIGHT CONTAIN THE CAUSATIVE AGENTS OF VIRAL HEPATITIS, ITS USE MUST BE CONSIDERED IN LIGHT OF THIS HAZARD, PARTICULARLY IN PERSONS WITH FEW PREVIOUS TRANSFUSIONS OF BLOOD AND PLASMA PRODUCTS.

Kasper and Kipnis[4] have concluded that those who had little exposure to blood products had 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 and plasma 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.

WARNING

Koāte™ concentrate is a purified dried fraction of pooled plasma obtained from many donors. *SINCE THE PRESENCE OR ABSENCE OF HEPATITIS VIRUS IN KOĀTE™ CONCENTRATE CANNOT BE PROVEN WITH ABSOLUTE CERTAINTY, THE PRESENCE OF SUCH A VIRUS SHOULD BE ASSUMED* and the hazard of administering Koāte™ concentrate should be weighed against the medical consequences of withholding it.

Since there is this definite risk of hepatitis, we suggest that the physician give consideration to explaining to the patient (or the patient's family) the relative risks of giving or withholding this product. Then, should the patient develop hepatitis, as a result of the injection, it will not come as a surprise, and there is not nearly the likelihood of resentment, which will almost surely follow an unexplained and unexpected infection.

PRECAUTIONS

1. Antihemophilic Factor (Human), 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. Antihemophilic Factor (Human), Koāte™, should be kept at a temperature below 8°C (46°F) until reconstituted for use. 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 should be used prior to administering the reconstituted Koāte™ solution. This may be accomplished using the enclosed sterile filter needle. See Reconstitution and Administration directions.

5. Koāte™ contains measurable 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

No severe adverse reactions were reported during the clinical trials of Koāte™. One patient experienced transient chest discomfort and cough beginning 20 minutes after infusion and lasting for one hour. During subsequent infusions this patient had no further reactions. A second patient developed transient dizziness following each of eight infusions. Mild allergic reactions may result from the administration of AHF preparations.

When large or frequently repeated doses are required in patients other than those of blood type O, there is a possibility of intravascular hemolysis. Should this condition occur leading to progressive anemia, administration of serologically compatible type O packed red blood cells should be considered[5]. Also the administration of type specific cryoprecipitate has been recommended for maintaining adequate Factor VIII levels[6].

DOSAGE

Each bottle of Koāte™ has the AHF activity in clinical units stated on the label of the bottle. One AHF unit is defined as the activity present in 1.0 ml of human plasma pooled from at least 10 donors and tested within three hours of collection of the first unit represented in the pool.

Dosage of Koāte™ required for normalizing hemostasis must be individualized according to the needs of the patient. The dose is dependent upon the weight of the patient, the severity of the deficiency, the severity of hemorrhage, the presence of inhibitors, and on the Factor VIII level desired. Abildgaard et al[7] have reported from studies in hemophilic children a linear dose-response relation with an approximate yield of 2 percent 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[8]. The following generalized dose schedule is suggested for various clinical situations:

1. Joint hemorrhages. If aspiration is not carried out, 10 units/Kg body weight should be administered at eight to twelve hour intervals for a period of one or more days depending on severity and patient response. The latter may be measured by relief of pain, swelling and restriction of joint movement. Early joint bleeds (associated with mild pain and minimal or no swelling), if treated promptly, may respond to a single dose of 10 units/Kg[8]. If aspiration is carried out, 10 units/Kg should be administered just prior to aspiration with a similar dose given six to eight hours later and repeated as necessary. Fully developed hemarthroses also may be treated with a single dose of 25 units/Kg aimed at achieving a Factor VIII level of 50%[9].

2. Muscle hemorrhages.

   A. Minor hemorrhages in the muscles of the extremities or trunk (non-vital areas). A dose of 10 units/Kg should be administered every eight to twelve hours until pain and swelling are relieved.

   B. Massive hemorrhages in non-vital areas. A dose of 10 units/Kg should be infused at eight to twelve hour intervals for two days or more, depending on relief of pain, improvement in hematocrit if this has fallen, and relief of other symptoms depending on the area of hemorrhage.

   C. Hemorrhages near vital organs (neck, throat, subperitoneal, etc.). A 20 unit/Kg dose should be administered initially, followed by 10 units/Kg every eight hours for 48 hours. Then half the dose should be administered at those time intervals for another 48 hours or more.

3. Overt bleeding. The initial dose should be 20 units/Kg followed by 10 units/Kg every eight hours for the first 24 hours, then every twelve hours for three to four days as necessary.

4. Massive wounds. Koāte™ should be infused until the bleeding stops. Then a maintenance dose of 20 units/Kg should be administered every eight hours. Levels of Factor VIII should be obtained and enough Koāte™ infused to maintain a minimum Factor VIII level of 40% in the patient.

5. Surgery[10,11,12]. Factor VIII levels of at least 40% are required for surgery. For surgery in the central nervous system even higher levels are recommended. Thirty to forty units/Kg body weight should be administered prior to surgery followed by 20 units/Kg every eight hours after surgery. This should be done with laboratory control, and the dosage should be increased if the Factor VIII level falls below 30% just prior to the next infusion. The postinfusion level should be approximately 60%, and it has been suggested that the Factor VIII level be raised to 30 to 40% of normal for at least ten days postoperatively[10]. For each unit of antihemophilic factor administered per Kg of body weight, a 2% rise in Factor VIII activity has been observed[7]. The following formulae can therefore be used to calculate approximately the expected response from a given dose or the dose required for a given effect:

$$\text{Expected Factor VIII increase (in \% of Normal)} = \frac{2.0 \times \text{units administered}}{\text{body weight (in Kg)}}$$

$$\text{Units required} = \text{body weight (Kg)} \times \text{desired Factor VIII increase (\% normal)} \times 0.5$$

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.

6. Prophylaxis. Experience with Factor VIII in the prophylactic management of severe hemophilia A has been published [13,14,15]. Kasper, et al[14] have recommended a dosage of 250 units of Factor VIII per day in the morning for patients weighing less than 50 Kg, and 500 units of Factor VIII for heavier patients. If bleeding episodes still occur too frequently, the daily dose is progressively increased until a satisfactory degree of protection is obtained.

The clinical effect of Factor VIII on the patient is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more Koāte™ than would be estimated in order to attain satisfactory clinical results. If the Factor VIII level fails to attain that expected, or if bleeding is not controlled after adequate calculated dosage, the presence of Factor VIII inhibitor should be suspected. By appropriate laboratory procedures the presence of an inhibitor can be substantiated and quantified thus allowing calculation of the amount of Factor VIII needed for its neutralization. When inhibitor is present, the dosage requirements for Factor VIII are extremely variable, and the dosage can be determined only by the clinical response.

RECONSTITUTION AND ADMINISTRATION

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

2. Remove the metal seals from both bottles to expose the central portions of the rubber stoppers and cleanse each stopper with a suitable antiseptic immediately before piercing. We recommend the following procedure: First swab the stopper with Iodine Tincture, U.S.P. followed by a sterile antiseptic swab.

3. With a sterile needle and syringe (filter needle supplied in package may be used) withdraw the appropriate volume of diluent (10 ml. or 20 ml. depending on Koāte™ package size) and transfer to the bottle of lyophilized Koāte™. The Koāte™ bottle is not sealed under vacuum. Add the Sterile Water for Injection, U.S.P. 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, leaving needle on the syringe 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. For additional bottles, the same syringe may be refilled through the filter needle.

STORAGE

Antihemophilic Factor (Human), Koāte™, must be stored under refrigeration (2°-8°C; 35°-46°F). Storage of lyophilized powder at room temperature for short periods, such as on trips, can be done without loss of Factor VIII activity. Freezing should be avoided as breakage of the diluent bottle might occur. Reconstituted Koāte™ should not be refrigerated and should be used within three hours of reconstitution.

HOW SUPPLIED

Antihemophilic Factor (Human), Koāte™, is supplied in single dose bottles with the total units of Factor VIII activity and total grams of protein stated on the label of each bottle. A suitable volume of Sterile Water for Injection, U.S.P., and a sterile filter needle is provided.

WARRANTY

We warrant that at the time of manufacture this product was prepared and tested in accordance with the standards and procedures recommended by the United States Food and Drug Administration and was true to label.

A number of factors beyond our control could reduce the efficacy of this product or even result in an ill effect following its use. These include storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biologic differences in individual patients. Because of these factors, *it is important that this product be stored properly and that the directions be followed carefully during use, and that the risk of transmitting hepatitis be carefully weighed before the product is prescribed.* The foregoing statement is made in lieu of any other warranty, express or implied, including any warranty of merchantability or fitness. Representatives of the Company are not authorized to vary the terms of this warranty or the contents of the printed labeling, including the package insert, for this product except by printed notice from the Company's Berkeley Office. *The prescriber and the user of this product must accept the terms hereof.*

REFERENCES

1. Hershgold EJ, Pool JG, Pappenhagen AR: The potent antihemophilic globulin concentrate derived from a cold insoluble fraction of human plasma: characterization and further data on preparation and clinical trial. J Lab Clin Med 67:23-32, 1966.

2. Deutsch E: Treatment of surgical complications in hemophilia in Hemophilia & Hemophillod Diseases. Chapel Hill, Univ. of N. Carolina Press: 1957, pp. 204-209.

3. Aggeler PM: Physiological basis for transfusion therapy in hemorrhagic disorders: A critical review. Transfusion 1:71-86, 1961.

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5. Rosati LA, Barnes B, Oberman HA, et al: Hemolytic anemia due to anti-A in concentrated antihemophilic factor preparations. Transfusion 10: 139-141, 1970.

6. Seeler RA: Hemolysis due to anti-A and anti-B in factor VIII preparations. Arch Intern Med 130:101-103, 1972.

7. Abildgaard CF, Simone JV, Corrigan JJ, et al: Treatment of hemophilia with glycine-precipitated factor VIII. N Engl J Med 275:471-475, 1966.

8. Britton M, Abildgaard C: New factor VIII concentrate: minimum dose for early bleed. Clin Res 21:303, 1973.

9. Honig GR, Forman EN, Johnston CA, et al: Administration of single doses of AHF (factor VIII) concentrates in the treatment of hemophilic hemarthroses. Pediatrics 43:26-33, 1969.

10. McMillan CW, Diamond LK, Surgenor DM: Treatment of classical hemophilia: The use of fibrinogen rich in factor VIII for hemorrhage and for surgery. N Engl J Med 265:224-230, 277-283, 1961.

11. Mazza JJ, Bowie EJW, Hagedorn AB, et al: Antihemophilic factor VIII in hemophilia: use of concentrates to permit major surgery. JAMA 211:1818-1823, 1970.

12. George JN, Brechenridge RT: The use of factor VIII and factor IX concentrates during surgery. JAMA 214:1673-1676, 1970.

13. Shanbrom E, Thelin GM: Experimental prophylaxis of severe hemophilia with a factor VIII concentrate. JAMA 208:1953-1956, 1969.

14. Kasper CK, Dietrich SL, Rapaport SI: Hemophilia prophylaxis with factor VIII concentrate. Arch Intern Med 125:1004-1009, 1970.

15. Lazerson J: The prophylactic approach to hemophilia A. Hosp Pract 6(2): 99-109, 1971.

LABELLING

We shall use the labels shown overleaf in the U.K. but they will be overprinted with our name, Bayer U.K. Ltd., Pharmaceutical Division, address Haywards Heath, Sussex, and the product licence number.

NDC

ANTIHEMOPHILIC FACTOR (HUMAN)

Koāte™

CUTTER

Lyophilized Powder Code

Dosage: See Direction Sheet

Store at 2° to 8°C. (35° to 46°F.).

CONTENTS:

One bottle of Koāte™
20 ml. Sterile Water for Injection, U.S.P.
One sterile filter needle for reconstitution

No Preservative

For Intravenous Administration Only

Sterile - Non-Pyrogenic

U.S. Gov't. Lic. No. 8

CUTTER Laboratories, Inc., Berkeley, Calif. 94710, U.S.A.

OPEN OTHER END

CARTON LABEL

FRONT PANEL

For reconstitution with
10 ml Sterile Water for
Injection, U.S.P.

016

Code

Lyophilized Powder

CUTTER

Koate™

ANTIHEMOPHILIC FACTOR (HUMAN)

Lot Exp.
_____ AHF Units *
_____ Grams Protein*

INSTRUCTIONS - RECONSTITUTION

1. Transfer 10 ml. of diluent to the bottle of lyophilized Koāte™.
2. After the diluent has been added, gently swirl the mixture until the powder is completely dissolved. Avoid foaming.
3. Withdraw the Koate™ solution through the filter needle which is enclosed.
4. Do not refrigerate after reconstitution.
5. Administer promptly after reconstitution within 3 hours.
6. See Direction Sheet for detailed instructions.

BACK PANEL

CARTON LABEL

For reconstitution with 10 ml.
Sterile Water for Injection, U.S.P.

*To be entered after potency assay is completed.

HEPATITIS DANGER
SEE DIRECTION
SHEET

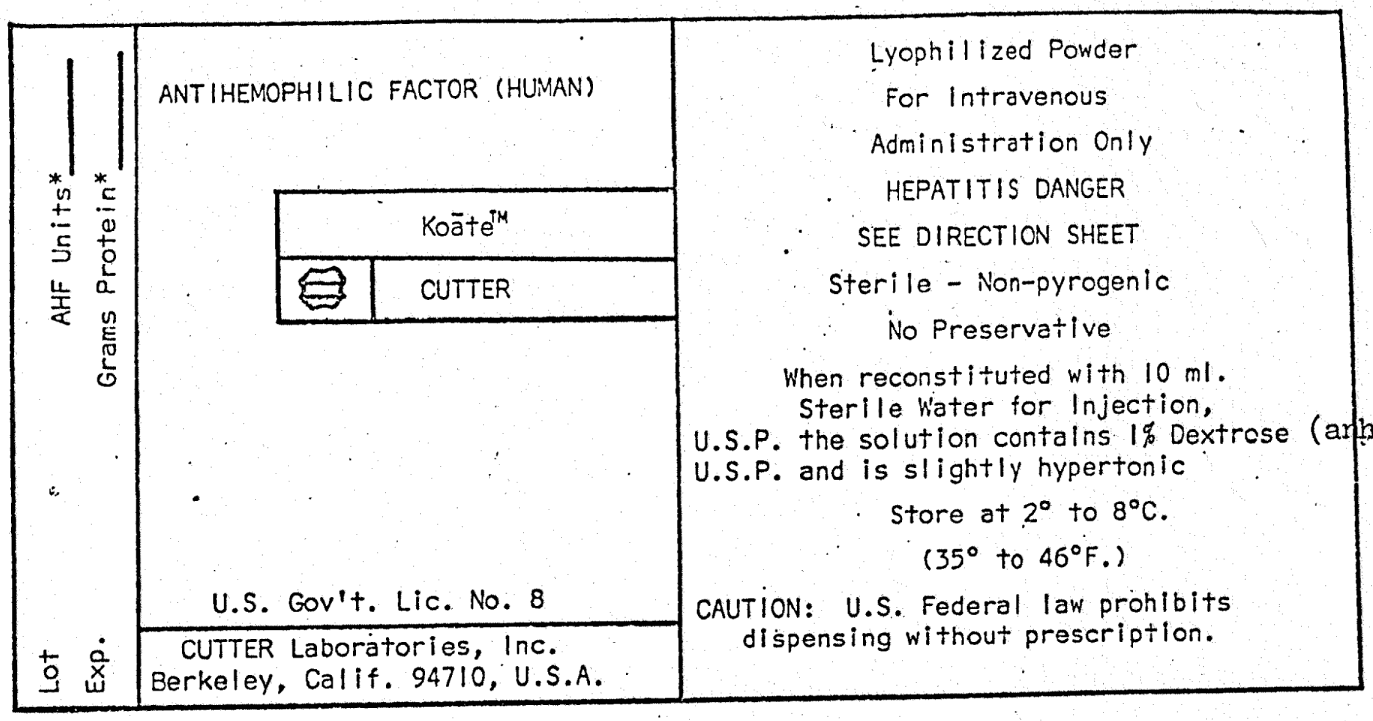
Not returnable for credit or exchange.

When reconstituted with 10 ml. Sterile Water for Injection, U.S.P. the solution contains 1% Dextrose U.S.P. (anhydrous) and is slightly hypertonic.

WARNING: Since the presence or absence of the virus of hepatitis in Koate™ cannot be proven with absolute certainty, the presence of such virus should be assumed and the hazard of administering Koate™ should be weighed against the medical consequences of withholding the use of Koāte™.

CAUTION: U.S. Federal law prohibits dispensing without prescription.

SIDE PANEL



CONTAINER LABEL

For Reconstitution with 10 ml.
Sterile Water for Injection, USP

* To be entered after potency assay is completed.

10/75

NDC

ANTIHEMOPHILIC FACTOR (HUMAN)

Koāte™

CUTTER

Lyophilized Powder Code

Dosage: See Direction Sheet

Store at 2° to 8°C. (35° to 46°F.).

CONTENTS:

One bottle of Koāte™
20 ml. Sterile Water for Injection, U.S.P.
One sterile filter needle for reconstitution

No Preservative

For Intravenous Administration Only

Sterile - Non-Pyrogenic

U.S. Gov't. Lic. No. 8

CUTTER Laboratories, Inc., Berkeley, Calif. 94710, U.S.A.

OPEN OTHER END

CARTON LABEL

FRONT PANEL

For reconstitution with 20 ml Sterile Water for Injection, U.S.P.

019

Code

Lyophilized Powder

CUTTER

Koate™

ANTIHEMOPHILIC FACTOR (HUMAN)

Lot

Exp.

____ AHF Units *

____ Grams Protein *

HEPATITIS DANGER
SEE DIRECTION
SHEET

INSTRUCTIONS - RECONSTITUTION

1. Transfer 20 ml. of diluent to the bottle of lyophilized Koate™.
2. After the diluent has been added, gently swirl the mixture until the powder is completely dissolved. Avoid foaming.
3. Withdraw the Koate™ solution through the filter needle which is enclosed.
4. Do not refrigerate after reconstitution.
5. Administer promptly after reconstitution within 3 hours.
6. See Direction Sheet for detailed instructions.

BACK PANEL

Not returnable for credit or exchange.

When reconstituted with 20 ml. Sterile Water for Injection, U.S.P. the solution contains 1% Dextrose, U.S.P. and is slightly hypertonic.

WARNING: Since the presence or absence of the virus of hepatitis in Koate™ cannot be proven with absolute certainty, the presence of such virus should be assumed and the hazard of administering Koate™ should be weighed against the medical consequences of withholding the use of Koate™.

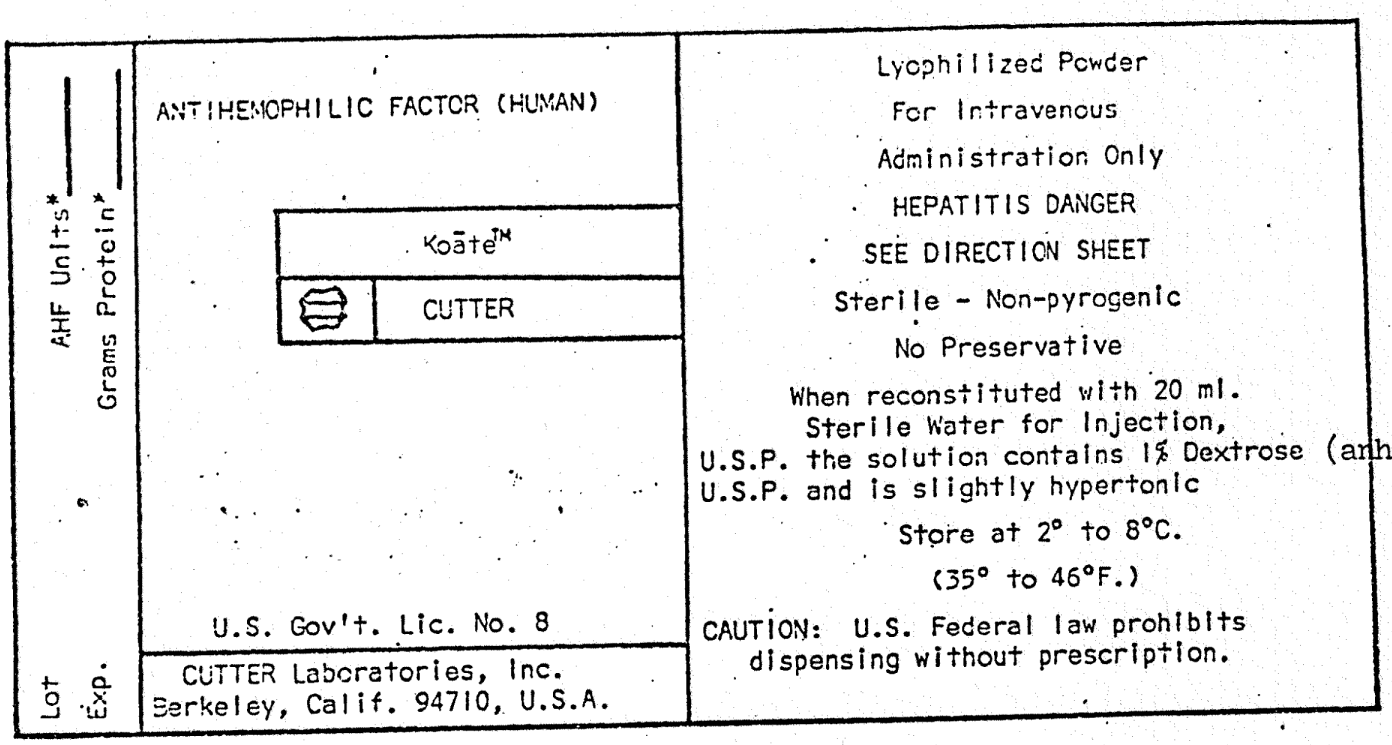
CAUTION: U.S. Federal law prohibits dispensing without prescription.

SIDE PANEL

CARTON LABEL

For reconstitution with 20 ml.
Sterile Water for Injection, U.S.P.

*To be entered after potency assay is completed.



CONTAINER LABEL

For Reconstitution with 20 ml.
Sterile Water for Injection, USP

*To be entered after potency assay is completed.

10/73

1

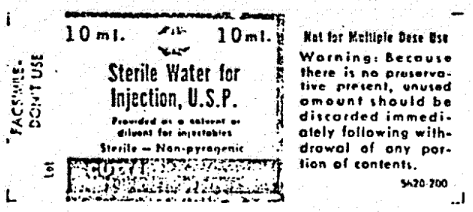
021

12-17

022

DILUENT CONTAINER LABEL

FILL: 10 ml.



DILUENT CONTAINER LABEL

Fill: 20 ml.